DOCUMENT RESUME

ED 478 366 CG 032 474

TITLE	A Collection of NIDA Notes: Articles That Address Research on Marijuana.
INSTITUTION	National Inst. on Drug Abuse (DHHS/PHS), Bethesda, MD.
REPORT NO	NN0058
PUB DATE	2003-07-00
NOTE	64p.
AVAILABLE FROM	For full text: http://165.112.78.61/NIDA_Notes/ NN0058.html.
PUB TYPE	Collected Works - General (020)
EDRS PRICE	EDRS Price MF01/PC03 Plus Postage.
DESCRIPTORS	Drug Abuse; Drug Rehabilitation; Illegal Drug Use; *Marijuana; Prevention; *Research

ABSTRACT

Included in this document are selections of topic-specific articles on marijuana research reprinted from the National Institute on Drug Abuse's (NIDA) research newsletter, NIDA Notes. The collection features articles originally published from 1995 through 2002. Topics include long-term cognitive impairments in heavy marijuana users, evidence that chronic marijuana users experience withdrawal upon quitting, the influence of genes and the environment on drug abuse vulnerability, the body's natural THC-like compounds, epidemiology, prevention, and treatment. (GCP)

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A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

RESEARCH ON MARIJUANA

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A Collection of

NIDA NOTES

NATIONAL INSTITUTE ON DRUG ABUSE

Articles That Address

Research on Marijuana

U.S. Department of Health and Human Services
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Introduction

The National Institute on Drug Abuse (NIDA) supports more than 85 percent of the world's research on drug abuse and addiction. NIDA-funded research enables scientists to apply the most advanced techniques available to the study of every aspect of drug abuse, including:

- genetic and social determinants of vulnerability and response to drugs;
- short- and long-term effects of drugs on the brain, including addiction;
- other health and social impacts of drug abuse, including infectious diseases and economic costs;
- development and testing of medication and behavioral treatments for abuse and addiction; and
- development and evaluation of effective messages to deter young people, in particular, from abusing drugs.

Included in this document are selections of topic-specific articles reprinted from NIDA's research newsletter, *NIDA NOTES*. Six times per year, *NIDA NOTES* reports on important highlights from NIDA-sponsored research, in a format that specialists and lay readers alike can read and put to use. Selections like the current one are intended to remind regular *NIDA NOTES* readers and inform other readers of important research discoveries during the periods they cover.

We hope the information contained here answers your needs and interests. To subscribe to *NIDA NOTES* and for further information on NIDA's drug abuse and addiction research, please visit our Web site at www.drugabuse.gov.

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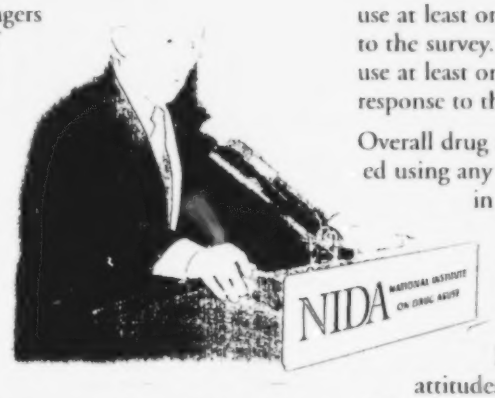
Research Findings

Vol 17, No 5 (January 2003)

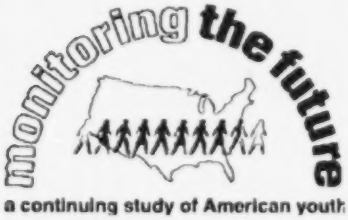
Teen Drug Use Declined in 2002, Report Shows

By Patrick Zickler *NIDA NOTES* Staff Writer

Drug use by American teenagers declined in a broad range of categories during 2002, according to the latest Monitor-ing the Future survey. Use of MDMA (ecstasy) dropped for the first time since it was added to the annual survey in 1996, and marijuana use declined to its lowest level in 8 years. The numbers of 8th- 10th- and 12th-graders who said they had smoked cigarettes in the month preceding the survey fell by 12 percent, 17 percent, and 10 percent, respectively.



"Our science-based education and prevention efforts are paying off," said NIDA Acting Director Dr. Glen Hanson at a press conference announcing the 2002 survey findings. "Teenagers are considering the information in the messages before deciding whether or not to use drugs, and they are making better decisions. In this survey we see that teenagers are increasingly choosing not to use marijuana, not to use ecstasy and other club drugs, not to begin smoking or using alcohol. They should be congratulated."



The Monitoring the Future survey (MTF) is conducted annually by the University of Michigan's Institute for Social Research and has been supported by NIDA throughout its 27-year history. The survey tracks illicit drug use and attitudes toward drugs among 8th-, 10th-, and 12th-grade students. The 2002 study surveyed a representative sample of more than 43,000 students in 394 schools across the Nation. Students are asked about their attitudes toward drugs (Do they perceive a risk associated with trying the drug? Do they approve or disapprove of someone's trying the drug?) and about lifetime, past-year, and past-month drug use. ("Lifetime" refers to use at least once during a respondent's lifetime. "Past year" refers to an individual's drug use at least once during the year preceding their response to the survey. "Past month" refers to an individual's drug use at least once during the month preceding their response to the survey.)

Overall drug use—the proportion of students who reported using any illicit drug in the preceding year—declined in grades 8 and 10. "This is the first time since 1998 that we have seen a significant decline in overall illicit drug use among 10th-graders," said Dr. Lloyd Johnston, MTF principal investigator.

MTF results for 2002 show that teenagers' attitudes about drugs are changing. Compared with 2001, this year more students in grades 10 and 12 said they believed use of MDMA once or twice is harmful, and the proportion of students who said they disapproved of trying MDMA increased in all three grades. "We are gratified, but not satisfied. NIDA will continue to generate and disseminate science-based information that leads to increases in understanding of the harm that comes from drug use," said Dr. Hanson.

"These changes in perceived risk and disapproval are encouraging indicators of future downturns in drug use," Dr. Johnston observed. "This has proven to be the case with ecstasy. In 2000, only 38 percent of seniors said there was great risk of harm associated with trying ecstasy. That jumped to 48 percent in 2001 and increased again to 52 percent in 2002. These unusually rapid changes no doubt reflect the effects of media coverage of adverse events as well as NIDA's efforts to document and disseminate information about the adverse consequences of using ecstasy."

Similarly, the decreases in smoking reported for 2002 follow increases in the proportion of students who perceived a negative image of smoking. Roughly half of students in all three grades said they strongly agree with the statement "I dislike being near people who are smoking." Perhaps more important to teens, Dr. Johnston noted, is the social implication of changing attitudes toward smoking. "Roughly three-quarters of boys and girls in all three grades said they prefer to date nonsmokers. It now appears that taking up smoking makes a youngster less attractive, just the opposite of what cigarette advertising has been promising."

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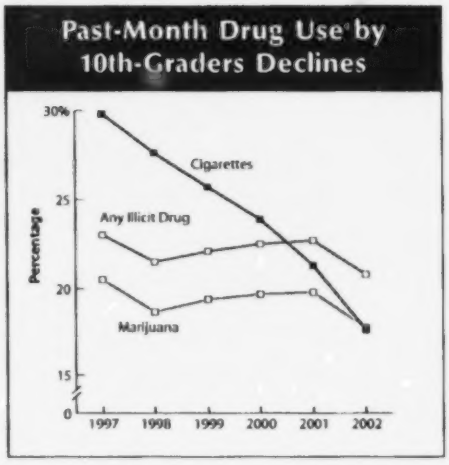
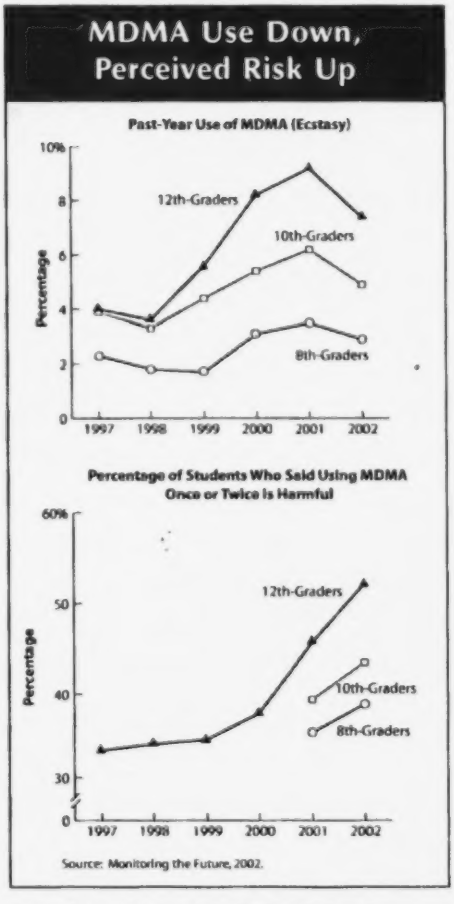
Significant changes reported in the 2002 MTF survey include the following:

- **Marijuana**—Among 10th-graders, marijuana use in the past year and past month decreased, and daily use in the past month was down. Past-year use decreased from 32.7 percent to 30.3 percent; past-month use went from 19.8 percent to 17.8 percent; and daily use in the past month declined from 4.5 percent to 3.9 percent.
- **Cocaine**—Crack use showed a significant increase in past-year use among 10th-graders, returning to around its 2000 level following a decline in 2001. For 2002, 2.3 percent of 10th-graders reported past-year use of crack cocaine, compared with 1.8 percent in 2001 and 2.2 percent in 2000.
- **Opiates**—For the first time, MTF asked students about nonmedical use of the prescription painkillers OxyContin and Vicodin. Past-year use of OxyContin without a doctor's order was reported by 1.3 percent of 8th-graders, 3.0 percent of 10th-graders, and 4.0 percent of 12th-graders. Nonmedical use of Vicodin in the past year was reported by 2.5 percent of 8th-graders, 6.9 percent of 10th-graders, and 9.6 percent of 12th-graders.
- **Inhalants**—Lifetime, past-year, and past-month use of inhalants decreased among 8th-graders, and lifetime use decreased among 10th-graders. Lifetime use went from 17.1 percent in 2001 to 15.2 percent in 2002 among 8th-graders and from 15.2 percent to 13.5 percent among 10th-graders.
- **LSD**—LSD showed major changes from 2001 to 2002. Rates of use decreased markedly in each grade and reporting period. Past-year use, for example, declined from 6.6 percent to 3.5 percent among 12th-graders, from 4.1 percent to 2.6 percent among 10th-graders, and from 2.2 percent to 1.5 percent among 8th-graders. These are the lowest rates of LSD use in the history of the survey for each grade.
- **Club Drugs**—Rates of MDMA (ecstasy) use decreased significantly among 10th-graders. Their past-year use declined from 6.2 percent to 4.9 percent, and past-month use went from 2.6 percent to 1.8 percent.

Findings from the 2002 MTF report are available through NIDA's Web site, www.drugabuse.gov, and at the MTF Web site, http://monitoringthefuture.org. NN



Monitoring the Future survey results show that teen drug use declined in 2002. Tenth-grade students reported significant reductions in overall drug use and in use of marijuana and cigarettes.



Use of MDMA (ecstasy) declined sharply among all teenagers in 2002, reversing 3 years of increased use. The decrease in use follows increased perception among teens that MDMA use has harmful consequences.

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Research Findings

Vol. 17, No. 3 (October 2002)

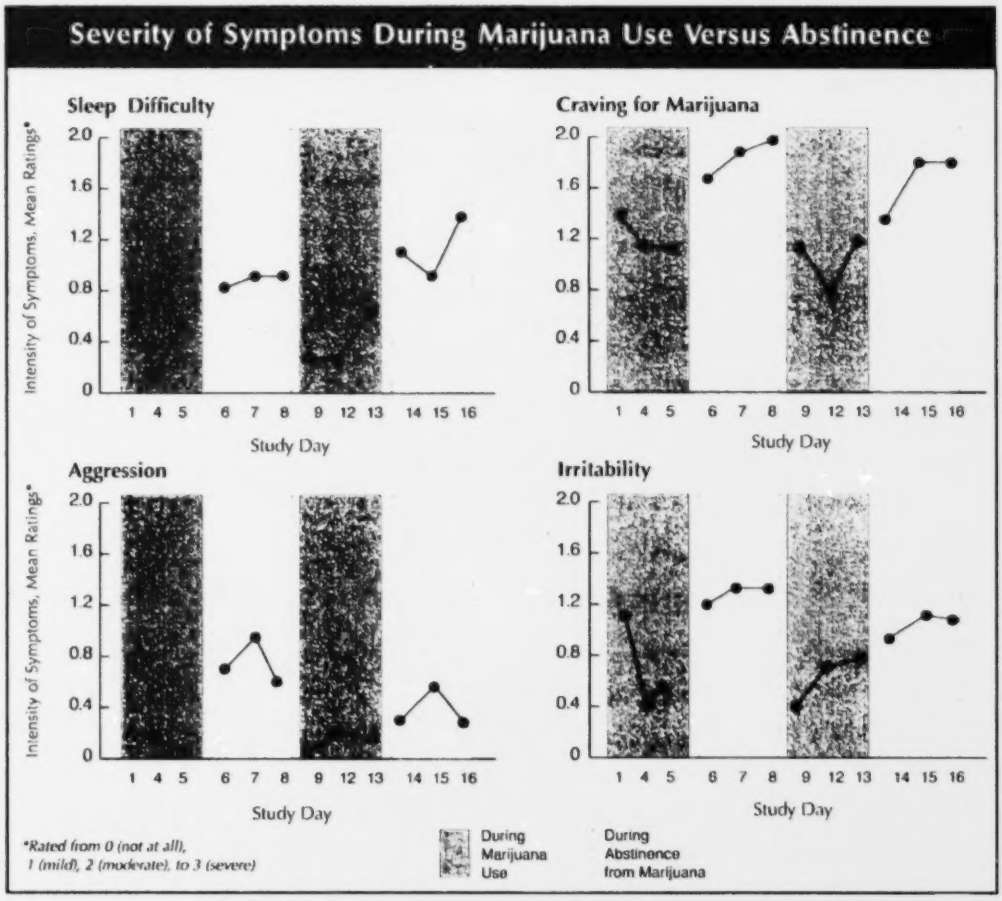
Study Demonstrates That Marijuana Smokers Experience Significant Withdrawal

By Patrick Zickler, *NIDA NOTES* Staff Writer

Animal research and controlled studies of marijuana smokers during inpatient treatment suggest that marijuana dependence, like dependence on other addictive drugs, is associated with withdrawal symptoms—such as irritability, anger, depressed mood, headaches, restlessness, lack of appetite, and craving—that can make it difficult to stop using the drug.

Now, NIDA-supported research conducted by Dr. Alan Budney and colleagues at the University of Vermont in Burlington has found that marijuana smokers who stop using the drug while in their home environment suffer withdrawal symptoms that appear as severe as those associated with tobacco-smoking.

"These findings represent a significant step toward general acceptance of withdrawal as a key aspect of chronic marijuana use," says Dr. Jag Khalsa of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. Treatment providers may not address the problem of



Marijuana smokers living at home reported "clinically significant" withdrawal symptoms—such as sleep difficulty, marijuana craving, aggression, and irritability—during periods of abstinence from the drug. The participants' self-reports were confirmed, in part, by observers who reported increased restlessness and irritability among the marijuana users when they were not smoking.

marijuana withdrawal because the condition is not currently included in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, the standard reference published by the American Psychiatric Association.

Dr. Budney and his colleagues evaluated withdrawal symptoms in 12 adult marijuana smokers (7 male, 5 female, average age 30 years) over 3-day abstinence periods that followed 5-day periods when participants could smoke marijuana at will. "We found consistent emotional and behavioral symptoms that increased during abstinence and dramatically decreased when marijuana smoking resumed, suggesting that these types of symptoms are the hallmark of acute marijuana withdrawal," Dr. Budney says. "The symptoms most closely resembled many of those observed during nicotine withdrawal."

During the study, participants lived at home and made daily records rating the intensity of withdrawal symptoms (on a scale from 0, "not at all," to 3, "severe") over the preceding 24 hours. In addition, each participant designated an observer—a friend or family member who spent at least 2 hours each day with the participant—to provide an independent rating of the participant's withdrawal symptoms. The participants made daily laboratory visits during which their abstinence was confirmed by urine tests.

During the abstinence periods, participants reported increases in the severity of craving and sleep difficulty, decreased appetite, and increased aggression, anger, and irritability. In addition, participants reported an increase in "strange dreams" during the second abstinence period. Observers reported increased irritability and restlessness among the participants during abstinence.

"Marijuana withdrawal doesn't include dramatic physical symptoms such as the pain, nausea, heavy sweating, and cramps associated with opiate withdrawal. Nevertheless, the symptoms of marijuana withdrawal appear clinically significant. It seems clear now that withdrawal from marijuana produces identifiable behavioral and emotional distress that may be as important as, if not more important than, physical symptoms in the development of dependence and undermining attempts to quit using the drug," Dr. Budney says.

"Confirming withdrawal as part of marijuana dependence will increase the likelihood that treatment providers will alert patients to its symptoms and will help them cope with it through behavioral or pharmacological treatments," says Dr. Khalsa.

Source

- Budney, A.J.; Hughes, J.R.; Moore, B.A.; Novy, P.L. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Archives of General Psychiatry* 58(10):917-924, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 3 (October 2002)

Cannabinoid Antagonist Reduces Marijuana's Effects in Humans

By Patrick Zickler, *NIDA NOTES* Staff Writer

Marijuana smokers treated with an experimental compound reported reduced highs and had smaller heart rate increases than untreated smokers in a recent study at NIDA's Intramural Research Program (IRP) in Baltimore. The finding confirms the pivotal role played in marijuana intoxication by certain structures—called cannabinoid receptors—on brain cells. In addition, the study suggests that the compound, called SR141716, may be useful as a medication to help marijuana smokers quit. (See also, "Study Opens Promising New Approach to Developing Medications To Prevent Relapse to Cocaine Use," in this issue).

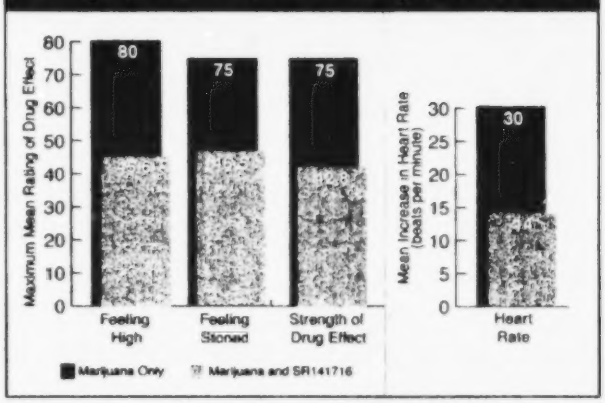
Marijuana, like other psychoactive drugs, achieves its effects by attaching to nerve cells in the brain and altering their function. The main psychoactive component of marijuana, tetrahydrocannabinol (THC), attaches to cannabinoid receptors. Animal studies have led scientists to believe that a particular type of cannabinoid receptor is the site at which THC initiates the effects that produce marijuana intoxication.

"Studies have shown in laboratory animals that the CB-1 cannabinoid receptors, which are found in high densities in regions of the brain associated with attention, motor control, and reasoning, play a major role in the effects of marijuana. However, until our study, this had not been confirmed in humans," says Dr. Marilyn Huestis, an IRP researcher.

To evaluate the role of human CB-1 receptors, Dr. Huestis and her colleagues studied the effects of SR141716 in 63 adult men with a history of smoking marijuana. The compound was developed by Sanofi-Synthelabo, Inc., of Malvern, Pennsylvania, and clinical testing of the compound in marijuana users was conducted through a Cooperative Research and Development Agreement with NIDA. SR141716 has effectively blocked the effects of marijuana at CB-1 receptors in studies involving rats, pigeons, and monkeys. Participants in the NIDA research received doses of 1, 3, 10, 30, or 90 mg SR141716 or placebo. Two hours later, they smoked a marijuana cigarette containing THC or a marijuana cigarette without THC. Immediately after smoking and up to 65 minutes later, participants rated the strength of marijuana's effects on a scale ranging from 0 (no effect at all) to 100 (extremely strong effect).

"Participants who received the 90-mg dose of SR141716 reported 40 to 75 percent less drug effect than those who didn't receive the compound. Those who received lower doses of the compound also reported less drug effect," Dr. Huestis says. "This demonstrates, first, that CB-1 receptors play a major role in THC's effects in humans and, second, that SR141716 can be used to at least partially block the drug's effects."

Compound Reduces Marijuana Effects



Participants received either placebo or active SR141716 before smoking marijuana and were then asked to describe, on a scale from 0 (not at all) to 100 (extremely), "How high do you feel now?" "How stoned on marijuana are you now?" and "How strong is the drug effect you feel now?" SR141716 (90 mg) reduced the maximum mean rating of the drug effects. Participants who received SR141716 also experienced smaller increases in heart rate after smoking marijuana.

In addition to its psychological effects on humans, marijuana increases the heart rate. Heart rates of men who smoked marijuana with THC but received no SR141716 increased by roughly 30 percent above baseline within 10 minutes of smoking marijuana and were 15 percent higher at 1 hour after smoking. Increases in heart rate after marijuana with THC was smoked were diminished in a dose-related manner by SR141716.

Blood tests showed that men who smoked marijuana with THC and who received 90 mg SR141716 had blood concentrations of THC similar to those of participants who did not receive SR141716. This demonstrates that reduction of marijuana's effects is attributable not to any effect of SR141716 on THC concentration, but to blockade of CB-1 receptors, Dr. Huestis says.

Because SR141716 partially blocks THC's intoxicating effects, the compound may prove valuable in treating

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marijuana addiction, the researchers say. If marijuana does not provide its usual high, patients in treatment would be less tempted to smoke it and less vulnerable to relapse. To evaluate the compound's role as a medication, NIDA researchers currently are studying SR141716's ability to reduce the effects of THC when given in repeated doses over 2 weeks. Other NIDA-supported research suggests that a different formulation of the compound may be effective in treatment of cocaine addiction (see this issue's "Study Opens Promising New Approach to Developing Medications To Prevent Relapse to Cocaine Use").

In addition, Sanofi-Synthelabo is investigating the compound's possible effects on other disorders related to cannabinoid receptors, such as increased appetite and food intake, and in smoking cessation treatment.

Source

- Huestis, M.A., et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Archives of General Psychiatry* 58(4):322-328, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 3 (October 2002)

New *Research Report* Presents Marijuana Facts

The latest in NIDA's *Research Report* series is "Marijuana Abuse," an eight-page pamphlet that summarizes current scientific knowledge of marijuana and its effects. "Today's marijuana is far more potent than the marijuana of 30 years ago," says NIDA Acting Director Dr. Glen R. Hanson. "The drug can produce a range of adverse physical and emotional effects, and—contrary to what many people believe—it can be addictive."

Acute Effects of Marijuana Use

Marijuana's effects start as soon as the drug enters the brain. The drug's mind-altering effects are caused by tetrahydrocannabinol (THC). Just a few minutes after inhalation of marijuana smoke, the user's heart rate accelerates, bronchial passages relax, and blood vessels in the eyes enlarge. Soon the user feels euphoric, experiencing pleasant sensations, colors, and sounds more intensely than usual. He or she may develop a dry mouth and feel very hungry or thirsty. When the euphoria passes, the user may feel sleepy or depressed. Sometimes marijuana use produces anxiety, fear, or panic in the wake of euphoria.

During marijuana intoxication, a user may have difficulty forming memories. THC also interferes with parts of the brain that control balance, posture, and coordination of movement.

With high doses of marijuana, the user may suffer toxic psychosis, including hallucinations, delusions, and a loss of the sense of personal identity. The specific causes are unknown, but toxic effects are more likely when a strong dose of THC is consumed in food or drink rather than smoked.

Long-Term Effects On Health

Marijuana has negative effects on memory and learning skills that are persistent but may not be permanent. Other effects of long-term abuse are cumulative and may last indefinitely. Regular marijuana smokers may have many of the same respiratory problems that tobacco smokers do: daily cough and phlegm production, frequent respiratory illness, a tendency toward obstructed airways, and a heightened risk of lung infections. Data suggest also that marijuana smoke increases the likelihood that head and neck cancers will develop, and it has the potential to promote lung cancer.

Some adverse effects may result from THC's impairing the immune system. In studies with mice, those exposed to THC or related substances were more likely than the unexposed animals to develop bacterial infections and tumors. In studies that used both animal and human cells exposed to marijuana ingredients, the normal disease-preventing actions of immune cells were inhibited.

A serious risk of long-term marijuana use is addiction—compulsive use of the drug, even though it interferes with family, school, and work. Withdrawal symptoms and drug craving can make it hard for long-term marijuana users to stop the drug. There are no medications to treat marijuana addiction, but behavioral therapies are available. Researchers are focusing on the most effective forms of counseling and incentives for abstinence.

Effects on School, Work, and Social Life

Students who smoke marijuana get lower grades than those who don't. Workers who smoke it are more likely to have problems on the job. Depression, anxiety, and personality disturbances are all associated with marijuana use. Marijuana interferes with a person's ability to learn and remember information, so frequent users may fall behind in developing intellectual, job, or social skills. Research with students has shown that marijuana use is linked to a reduction in the psychological skills that enable individuals to maintain confidence and persist in their pursuit of goals.

For More Information

"Marijuana Abuse" can be ordered from the National Clearinghouse for Alcohol and Drug Information; call 800-729-6686 (800-487-4889 for the deaf) or order online at www.health.org. Ask for publication #PHD940. NN

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 2 (May 2002)

Shortened Family Prevention Programs Yield Long-Lasting Reductions in Adolescent Drug Abuse

By Robert Mathias, *NIDA NOTES* Staff Writer

Two brief family-focused drug abuse prevention programs have produced long-term reductions in substance abuse among adolescents in rural Iowa public schools who were assigned to the programs in the sixth grade, a study funded by NIDA and the National Institute of Mental Health has shown. The programs may offer communities a practical approach to effective family-based drug abuse prevention.

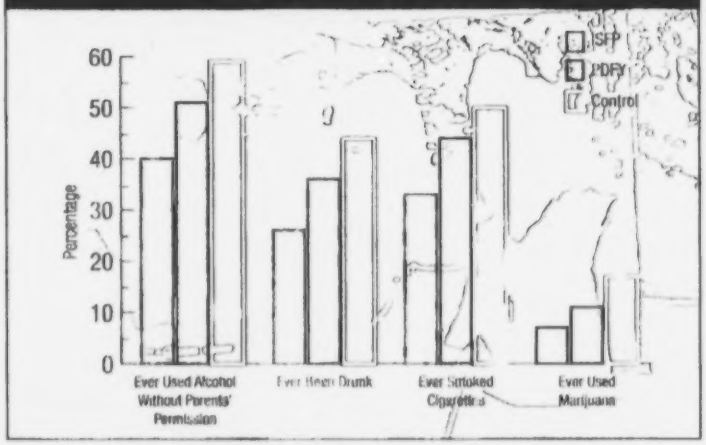
The longer of the two programs reduced the proportion of students who used any marijuana, tobacco, or alcohol in grades 6 through 10 as well as students' current use of alcohol and tobacco. The shorter program decreased alcohol use among 10th-graders significantly, along with reducing lifetime substance use behaviors.

"The study demonstrates that brief family interventions can reduce drug use among young people during the high-risk years when they are making the transition from childhood to adolescence," says Dr. Richard Spoth of Iowa State University in Ames, who led the study. Reducing the number of children who begin substance use during these years may have important public health benefits because early initial use is associated with higher rates of substance dependence in later adolescence and young adulthood, he says.

A total of 667 families of sixth-graders from 33 public schools in Iowa were recruited for the study. The children's schools were randomly assigned to either a five-session program called Preparing for the Drug Free Years (PDFY), a seven-session Iowa Strengthening Families Program (ISFP), or a control group. The two programs were designed for families with young adolescents. The ISFP was adapted from a more extensive program that had previously been evaluated in a variety of settings and with several racial and ethnic groups.

"The purpose of modifying longer programs and trying to replicate their results in new settings is to make them more practical for communities to implement and for families to participate in them," notes Dr. Elizabeth Robertson of NIDA's Division of Epidemiology, Services and Prevention Research. "The fact that the adapted programs achieved very positive results indicates they can be whittled down and still maintain their effectiveness," she says.

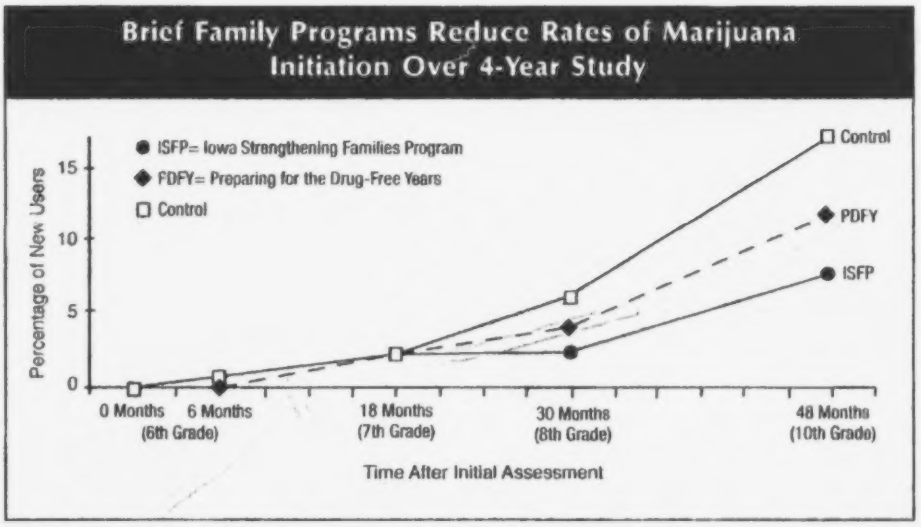
Substance Use Behaviors Among 10th-Grade Students



Lower percentages of ISFP and PDFY 10th graders than control students had initiated a number of substance abuse behaviors involving use of alcohol, cigarettes, and marijuana 4 years after they had received the programs in the 6th grade.

Staff members from the Iowa Cooperative State Research, Education, and Extension Service of the U.S. Department of Agriculture worked with community facilitators to implement either PDFY or ISFP in a total of 22 schools with 459 families whose family, school, and community characteristics had previously been assessed. Eleven schools with 208 comparable families were assigned to a control group that was mailed leaflets on adolescent development and parent-child relationships. The programs were delivered in weekly evening sessions to participating families at the schools. Parents in PDFY attended four sessions and were joined by their children for a final joint session. In the relatively more intensive ISFP, parents and children attended both separate and joint sessions for 6 weeks and a final joint session. The weekly PDFY and ISFP sessions sought to improve how parents and children functioned individually and as a family in a variety of situations. Both programs taught skills such as effective parenting, appropriate management of family conflicts, and how to resist peer pressure. The development of such skills has been linked to delayed onset or reduction of substance abuse.

Four years after 6th-grade students had received the programs, the researchers interviewed them and found that



Initiation of marijuana use occurred at a slower rate among students who participated in the ISFP and PDFY programs than among those in the control group.

significantly lower percentages of ISFP than control 10th-graders had ever initiated any of five substance abuse behaviors. Specifically, lower percentages of ISFP students than controls had begun to use alcohol, cigarettes, or marijuana; had ever used alcohol without parental permission; or had become drunk. The proportion of new marijuana users in the control group was 2.4 times greater than it was among ISFP youths. Similarly, the proportion of controls who had been drunk or smoked cigarettes were 1.7 and 1.5 times greater than they were among ISFP youths. Participants in the PDFY program also showed lower rates of initiation of all five substance use behaviors than controls, but only the differences in lifetime drunkenness and marijuana use approached statistical significance. Nevertheless, the rates of new marijuana use and ever getting drunk were 1.5 and 1.2 times greater for controls than they were for PDFY youths. Actual rates of substance use behaviors among 10th-graders in all three groups are shown in the illustration on the preceeding page.

Among those 10th-graders in the three groups who had begun to use alcohol, tobacco, or marijuana, the study found lower proportions of PDFY and ISFP students than controls had used alcohol and tobacco in the preceding month and marijuana during the preceding year. For example, frequency of past-month alcohol use among PDFY and ISFP students was about two-thirds that of controls. Among ISFP students, past-month cigarette use was approximately half that of control group students.

"Developmental timing is an important factor in the long-term effects of these interventions," Dr. Spoth says. "Intervening at this time, in the sixth grade when kids are experimenting with substances, probably contributes greatly to the positive effects," he says. The careful design of the interventions with their theory-based focus on parenting and family interactions also is important, he adds.

The critical element affected by both programs is the parent component, says NIDA's Dr. Robertson. "When you provide parents with information about what to expect of children at that age, what is typical and what is not, and how to deal with some of the problems, you are shaping how parents relate to their children. Changing the family context can have a long-lasting effect because you are positively influencing the day-to-day environment of the child over a long period of time," she says.

Whether the findings of this study would apply to more diverse populations in other settings remains an open question, Dr. Robertson says. However, the original programs from which the critical elements in these programs were derived have been successfully tested in a variety of settings, she notes. In addition, the ISFP has been adapted for and is now being tested with urban and rural African-Americans and Native American families.

Source

- Spoth, R.L.; Redmond, C.; and Shin, C. Randomized trial of brief family interventions for general populations: Adolescent substance use outcomes 4 years following baseline. *Journal of Consulting and Clinical Psychology* 69(4):627-642, 2001. NN

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 1 (April 2002)

Chronic Marijuana Abuse May Increase Risk of Stroke

Dr. Ronald I. Herning and Dr. Jean Lud Cadet, with colleagues at NIDA's Intramural Research Program in Baltimore, report preliminary evidence suggesting that chronic abuse of marijuana can restrict blood flow to the brain and increase the risk of stroke for young men aged 18 to 30.

The investigators used transcranial Doppler sonography, a noninvasive technology that uses sound waves to take measurements and create images, to calculate the pulsatility index—a measure of resistance to blood flow—in cerebral arteries of 35 male participants, 16 long-term marijuana users and 19 nonusers of marijuana. Marijuana users had higher resistance to blood flow to their brains than did nonusers upon initial measurement, and the deficits persisted after the marijuana abusers remained abstinent for a month, well past the time when acute withdrawal symptoms were reported. As a result, the deficits do not appear to be related to a temporary withdrawal syndrome.

The findings suggest that, at least within the first 4 weeks of marijuana abstinence, blood flow in the brain in young marijuana abusers is comparable to that of 60-year-olds, which may be of clinical importance because advancing age increases the risk of stroke. NN

The study was published in the June 2001 *Annals of the New York Academy of Science.*

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 1 (April 2002)

Cognitive Deficits Associated With Heavy Marijuana Use Appear To Be Reversible

By Margi Grady, *NIDA NOTES* Contributing Writer

Memory and learning problems caused by heavy marijuana smoking persist for at least a week after cessation of use of the drug, but they appear to resolve completely within a month, a NIDA-supported study shows. "Cognitive impairment from heavy marijuana use may linger for a week or longer, but it does not appear to be permanent," says Dr. Harrison Pope, Jr., who led the study at Harvard University's McLean Hospital in Belmont, Massachusetts. "Even if users smoke a lot, these tests suggest they can eventually recover," he says. As a followup to this research, Dr. Pope and his colleagues are using functional magnetic resonance imaging to determine whether the more sensitive assessment tool reveals cognitive effects that his pencil-and-paper tests could not detect.

Heavy Marijuana Users Report Lower Income And Less Education Than Control Subjects

	Current Heavy Users (N=63)	Former Heavy Users (N=45)	Control Subjects (N=72)
Education	**Percentage**		
Education, High School or Less	29%	13%	0%
Mother's Education, High School or Less	61	40	58
Father's Education, High School or Less	46	50	38
Household Income			
Household Income Less Than $30,000	51	51	26
Parents' Household Income Less Than $30,000	25	44	18

Information gathered on the Harvard study's participants revealed that both current and former long-term heavy users of marijuana had markedly lower income and less education than control subjects, even though the education and income of the two groups' parents were similar, says Dr. Harrison Pope, Jr., the study's lead investigator.

"Even though our study suggests that heavy users recover from cognitive deficits after 4 weeks of abstinence, it doesn't follow that marijuana is a benign substance," says Dr. Pope. He notes that the study revealed some startling demographic differences between long-term heavy users and a control group. Data collected on participants when they joined the study showed that those who had used marijuana heavily for many years had markedly lower income and education levels than the control group, regardless of whether they were still using the drug.

Dr. Pope and his colleagues examined cognitive function in 180 participants, including 63 current heavy marijuana users, 45 former heavy users, and 72 control subjects. Current heavy users had smoked marijuana a minimum of 5,000 times during their lives (the equivalent of at least once a day for 13 years) and were smoking at least 7 times a week at the beginning of the study. Former heavy users had also smoked at least 5,000 times in their lives but no more than 12 times during the previous 3 months. The control subjects had smoked at least once but no more than 50 times during their lives and no more than once in the previous year. Participants ranged in age from 30 to 55. All three groups were carefully screened for unrelated characteristics that might affect the study results.

All participants were required to remain abstinent from marijuana and other drugs for the course of the 28-day study and submit urine specimens that were used to confirm their abstinence. Their cognitive function was evaluated through standardized neuropsychological tests at study entry and on the 1st, 7th, and 28th days of the study. On study entry (day 0) and days 1 and 7, current heavy marijuana users scored significantly lower than control subjects on tests of verbal learning and memory. This finding confirms and extends the findings of previous studies by Dr. Pope's group and others that have shown impaired cognitive skills in heavy marijuana users for up to 3 days after use is stopped. By day 28, the difference between the scores of the control group and those of current heavy marijuana users disappeared.

Income and education data suggest consequences of heavy marijuana use.

Two findings allowed the researchers to conclude that the cognitive deficits were associated with recent heavy use rather than total lifetime use. First, former heavy users showed no significant difference from the control subjects on any of the tests on any of the testing days. Also, the researchers found a clear relationship between lower test

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scores and higher levels of marijuana residues in urine at the beginning of the study, but no relationship between test scores and total lifetime marijuana use.

"This study is particularly significant for treatment," says Dr. Steven Grant of NIDA's Division of Treatment Research and Development. "By stopping drug use, heavy marijuana users are able to regain their memory and learning functions. Still, we cannot say there are no consequences to heavy marijuana use: The income and education data suggest the opposite."

Sources

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- Solowij, N. *Cannabis and Cognitive Functioning.* Cambridge, UK: Cambridge University Press, 1998. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Vol. 17, No. 1 (April 2002)

Adolescent Treatment Programs Reduce Drug Abuse, Produce Other Improvements

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

In the first large-scale study designed to evaluate drug abuse treatment outcomes among adolescents in age-specific treatment programs, NIDA-supported researchers have found that longer stays in these treatment programs can effectively decrease drug and alcohol use and criminal activity as well as improve school performance and psychological adjustment.

The study, part of NIDA's ongoing Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A), analyzed data from 23 community-based adolescent treatment programs that addressed peer relationships, educational concerns, and family issues such as parent-child relationships and parental substance abuse. Successful elements of adult treatment programs, such as participation in group therapy and participation in a 12-step program, were also included in treatment plans.

"The results of this study are particularly impressive in light of the fact that the adolescents had multiple problems," says Dr. Christine Grella of the University of California, Los Angeles (UCLA), Drug Abuse Research Center, one of the study's investigators. "Although this is also typical of many adults in treatment, timely resolution of these problems is even more critical for adolescents. These young people are in the process of developing values, making lifestyle decisions, and preparing to assume adult roles and responsibilities, such as family and work; whereas when many adults enter treatment, they have completed this process."

Behaviors of Adolescents Before and One Year After Treatment

	Before	After
DRUG USE	Percentage	
Weekly Marijuana Use	80.4%	43.8%
Heavy Drinking	33.8	20.3
Hallucinogen Use	31.0	26.8
Stimulant Use	19.1	15.3
SCHOOL PERFORMANCE		
Regular Attendance	62.6	74.0
Grades Average or Better	53.4	79.6
CRIMINAL ACTIVITIES		
Any Illegal Act	75.6	52.8
Any Arrest	50.3	33.9

An evaluation of more than 1,100 adolescents who received substance abuse treatment in residential, short-term inpatient, or drug-free outpatient programs found improvement in rates of drug use and social behavior. Some 53 percent of those treated met or exceeded the minimum recommended stay in treatment.

Treatment Programs Varied

Dr. Yih-Ing Hser, also of UCLA, led the research team that evaluated the treatment outcomes for 1,167 adolescents, age 11 to 18, who were admitted to one of the treatment programs between 1993 and 1995. The treatment centers, located in Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Chicago, Illinois; and Portland, Oregon, included eight residential programs, nine outpatient drug-free programs, and six short-term inpatient programs.

The 418 adolescents in the residential treatment programs received education, individual and group counseling, and interventions to develop social responsibility. The 292 adolescents in the outpatient drug-free programs received education, skills training, and individual and group counseling. The 467 adolescents in short-term inpatient programs received counseling and a 12-step program. Family therapy was strongly emphasized, and adolescents in these programs were referred to continued outpatient treatment. The average length of treatment for adolescents in the residential, outpatient drug-free, and short-term inpatient programs was 5 months, 1.6 months, and 18 days, respectively.

The adolescents were interviewed when they began treatment and again 1 year after discharge by professional interviewers who were not employed by the treatment centers. Problem severity was determined at the initial interview according to a number of criteria. Dependence on drugs or alcohol was determined from standardized diagnostic measures. To validate self-reports of drug use, one-quarter of the participants were selected randomly to submit urine samples during the posttreatment interview.

Before treatment, 25 percent of the participants used three or more drugs, 36 percent were dependent on alcohol,

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In the year following treatment, more adolescents attended school and reported average or better-than-average grades.

64 percent were dependent on marijuana, and 10 percent were dependent on cocaine. In addition to substance abuse problems, 63 percent were diagnosed with a mental disorder and 67 percent were criminally active.

Outcomes Overall

Research has indicated that in general the rate of drug and alcohol use tends to increase during adolescence. In the present study, however, improvements were observed in many of the areas evaluated, although some of the participants did not complete their treatment program. Comparing the year before treatment to the year after treatment, the adolescents showed significant declines in the use of marijuana and alcohol, which are considered to be the major drugs of abuse for this age group. Weekly or more frequent marijuana use dropped from 80 percent to 44 percent, and abstinence from any use of other illicit drugs increased from 52 percent to 58 percent. Heavy drinking decreased from 34 percent to 20 percent, and criminal activity decreased from 76 percent to 53 percent. Adolescents also reported fewer thoughts of suicide, lower hostility, and higher self-esteem. In the year following treatment, more adolescents attended school and reported average or better-than-average grades. Some exceptions to the general pattern of improvement were that overall, cocaine and hallucinogen use did not improve during the year after treatment.

Treatment Length and Outcomes

Previous research indicates that a minimum of 90 days of treatment for residential and outpatient drug-free programs and 21 days for short-term inpatient programs is predictive of positive outcomes for adults in treatment. Better treatment outcomes were reported among adolescents who met or exceeded these minimum lengths of treatment than for those who did not. Among the treatment participants, 58 percent of those in residential programs, 27 percent in outpatient drug-free programs, and 64 percent in short-term inpatient programs met or exceeded the minimum stay. In the year following treatment, those who met or exceeded the minimum treatment were 1.52 times more likely to abstain from drug and alcohol use and 1.2 times more likely to not be involved in criminal activity. In addition, these adolescents were 1.34 times more likely to have average or better-than-average grades.

This study confirms that community-based drug treatment programs designed for adolescents can reduce substance abuse and have a positive impact on many other aspects of their life, says Dr. Tom Hilton of NIDA's Division of Epidemiology, Services and Prevention Research. These results justify new research to identify the key elements common to effective treatment programs for adolescents, he noted.

Source

- Hser, Y-I.; Grella, C.E.; Hubbard, R.L.; et al. An evaluation of drug treatment for adolescents in four U.S. cities. *Archives of General Psychiatry* 58(7):689-695, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 16, Number 4 (October 2001)

Television Public Service Announcements Decrease Marijuana Use in Targeted Teens

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

NIDA-supported researchers have helped clarify the necessary elements in effective anti-drug public service announcements (PSAs) directed at high-sensation-seeking adolescents.

NIDA researchers have previously shown that high-sensation-seekers—individuals characterized by their need for new, emotionally intense experiences and the willingness to take risks to obtain these experiences—are at greater risk for using marijuana and other drugs and for using them at an earlier age than other individuals.

Using a prevention approach developed from previous NIDA-supported studies, the researchers produced five anti-marijuana PSAs. The dramatic and attention-getting PSAs were aired during programs that appealed to high-sensation-seekers such as action-oriented television shows. The media placement was supported by paid as well as donated advertising to ensure the most effective outreach to the target audience.

Drs. Philip Palmgreen (left) and Lewis Donohew review a public service announcement at the University of Kentucky.

"To appeal to high-sensation-seekers, a PSA must be dramatic, intense, and highly original," says Dr. Philip Palmgreen, the research team leader at the University of Kentucky in Lexington. "An effective PSA needs to show the negative consequences that can occur as a direct result of drug use. For example, high-sensation-seekers need to see that they can end up in a wheelchair, lose their job, or lose their girlfriend or boyfriend as a result of drug use. We found that the threat of death is not a deterrent because high-sensation-seekers do not believe that death is a real possibility," he says.

The PSAs were aired from January through April 1997 in Fayette County, Kentucky, and from January through April 1998 in Fayette County and Knox County, Tennessee. One hundred students in 7th through 10th grade were selected each month by random phone calls and asked to participate in the study. The students were interviewed to determine whether they saw the PSAs and their attitudes toward and whether they used marijuana and other drugs. Questions also were asked to determine their degree of sensation-seeking. More than 70 percent of the targeted age groups watched at least three PSAs per week, the researchers say.

Marijuana use declined substantially among teens during the campaigns in both counties and residual effects of the campaigns were evident for several months. According to Dr. Palmgreen, the second campaign in Fayette County had a "booster effect," resulting in further declines. Overall, marijuana use decreased by 38 percent in Fayette County. In Knox County, marijuana use declined among high-sensation-seeking teens by 26.7 percent.

"We have shown that, for PSAs to be effective, they must be designed for a specific audience and must air frequently during programs watched by that audience," says Dr. Palmgreen. "PSAs typically are shown during donated airtime. However, the trend toward paid placements of PSAs, as in various campaigns across the country, is a very positive approach."

Source

- Palmgreen, P.; Donohew, L.; Lorch, E.P.; Hoyle, R.; and Stephenson, M.T. Television campaigns and adolescent marijuana use: Tests of sensation seeking targeting. *American Journal of Public Health* 91(2):292-296, 2001. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE
Research Findings
Volume 16, Number 3 (August 2001)

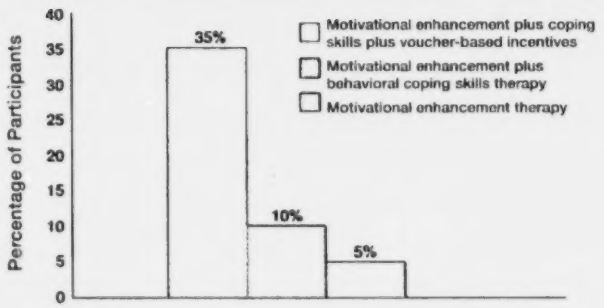
Adding Vouchers to Behavioral Therapies Improves Marijuana Treatment Results

Enhancing behavioral treatments by adding the opportunity to earn vouchers for remaining drug-free has been shown to improve abstinence rates among cocaine- and opiate-addicted patients. Now, a NIDA-funded study has shown that the combination of behavioral interventions and voucher-based incentives also can improve treatment results for heavy marijuana abusers.

Researchers at the University of Vermont in Burlington, led by Dr. Alan J. Budney, recruited 60 heavy marijuana users who wanted to quit. Most of the study participants had long histories of marijuana abuse, smoked marijuana almost daily, and smoked more than once a day. They were randomly assigned to one of three treatments: motivational enhancement therapy, motivational enhancement plus behavioral coping skills therapy, or motivational enhancement plus coping skills plus voucher-based incentives. Throughout the study, each participant gave urine samples twice weekly to be tested for marijuana use. If patients in the incentives group tested negative, they earned vouchers that they could exchange for retail goods or services, such as movie passes, sporting equipment, or vocational classes. Patients in the other two treatment groups did not receive such tangible rewards for abstinence.

Over the 14-week study, 40 percent of patients in the incentives group achieved at least 7 weeks of continuous abstinence from marijuana, compared with 5 percent of patients in each of the other groups. At the end of the treatment period, 35 percent of the incentives group had stopped using marijuana, compared to 10 percent of the motivational enhancement plus coping skills group and 5 percent of the motivational enhancement group.

Marijuana Abstinence at End of Treatment



Adding voucher-based incentives to behavioral and motivational treatments more than tripled the percentage of patients who stopped using marijuana by the end of treatment.

The study was published in the December 2000 issue of the *Journal of Consulting and Clinical Psychology.* NN

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

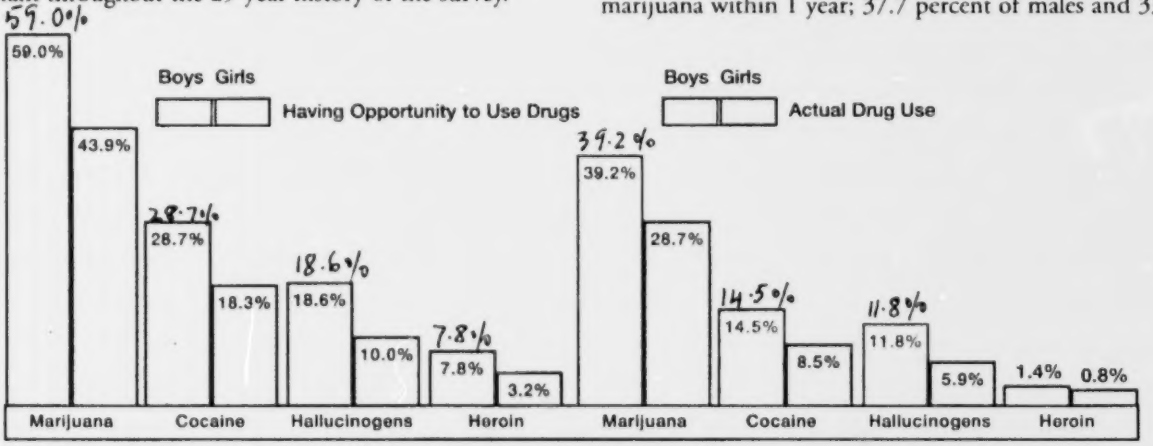
Research Findings

Volume 15, Number 4 (September 2000)

Gender Differences in Prevalence of Drug Abuse Traced to Opportunities to Use

By Patrick Zickler, *NIDA NOTES* Staff Writer

Males are more likely than females to abuse drugs. According to the 1999 National Household Survey on Drug Abuse (NHSDA)—an annual Substance Abuse and Mental Health Services Administration survey of more than 25,000 respondents—8.1 percent of males and 4.5 percent of females older than age 12 had used illicit drugs within the past month, and this ratio has remained fairly constant throughout the 29-year history of the survey.



According to the 1993 National Household Survey on Drug Abuse, boys are more likely to abuse drugs than girls. The graph above shows the estimated percentage of boys and girls using each drug and the percentage having the opportunity to use each drug.

Research by Dr. James Anthony, a NIDA-supported scientist at the Johns Hopkins University School of Hygiene and Public Health in Baltimore, shows that these gender differences in drug abuse are not related to gender differences in susceptibility. Instead, they have their foundation in the very first stage of drug involvement—the opportunity to use drugs. Once given the opportunity to use, males and females are equally likely to use drugs.

Dr. Anthony and his colleagues analyzed NHSDA data for 1993 to look for information that might explain the gender difference in rates of drug abuse. "Males are more likely than females to have an opportunity to use drugs. There is no male-female difference with respect to trying a drug once an opportunity to do so has been experienced," Dr. Anthony says.

The findings are consistent for marijuana, cocaine, hallucinogens, and heroin, Dr. Anthony says. The proportion of opportunities to use marijuana was 59 percent of males compared with 43.9 percent of females; to use cocaine, 28.7 percent of males and 18.3 percent of females; to use hallucinogens, 18.6 percent of males and 10 percent of females; and to use heroin, 7.8 percent of males and 3.2 percent of females.

Once presented with an opportunity to use drugs, 44.2 percent of males and 42 percent of females began using marijuana within 1 year; 37.7 percent of males and 33.2 percent of females began using cocaine; 50.5 percent of males and 50 percent of females began using hallucinogens; and 14.6 percent of males and 22.1 percent of females began using heroin.

Dr. Anthony found that females were likely to get their first opportunity to use cocaine at an earlier age than were males (age 19 for females, age 20 for males) but that there were no differences among males and females in age of first opportunity to use marijuana, heroin, or hallucinogens.

One benefit of improved understanding of the link between opportunity and eventual use is that counselors or physicians may be able to learn about young patients' drug use by asking about their opportunities to use drugs. "Young people may feel freer to answer a question about the opportunity to use drugs rather than a question about actual drug use, because the opportunity is less likely to be illegal or particularly sensitive," Dr. Anthony says.

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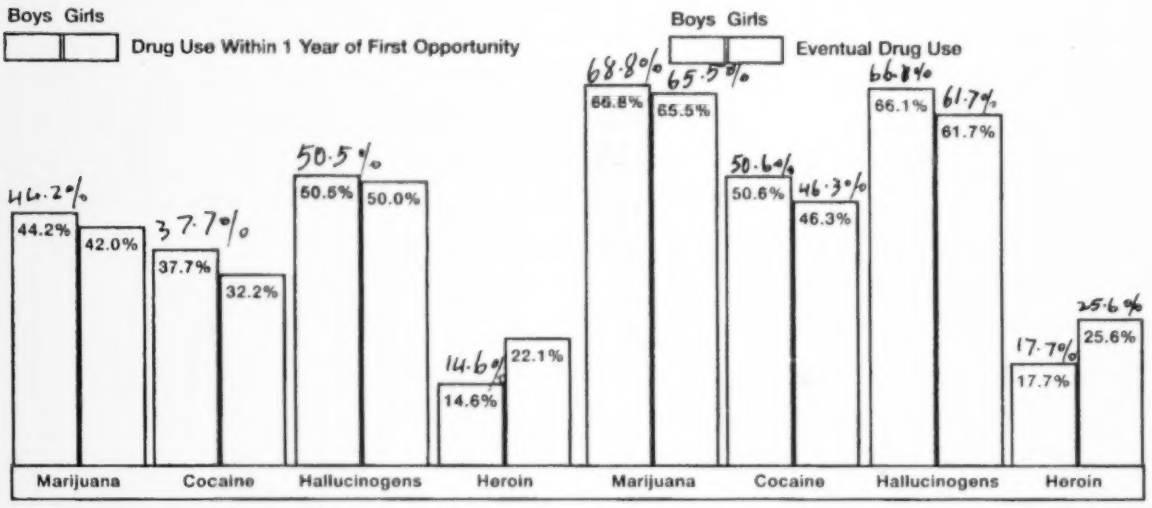

This graph shows the percentage of drug use within 1 year of the first opportunity to use drugs and the percentage of boys and girls to eventually use drugs, given the opportunity.

Understanding the differences in opportunities to use drugs may also help shape prevention efforts, according to Dr. Cora Lee Wetherington, NIDA's Women and Gender Research Coordinator. "The prevalence of drug abuse is greater for males than for females even though, given the initial opportunity to use drugs, males and females are equally likely to move on to drug use. It appears that the opportunities themselves play a very important role in drug abuse and need more investigation. Understanding the sex differences in opportunities could make it possible to develop prevention programs that reduce the opportunities and, therefore, the higher rate of drug abuse among males. In fact, NIDA-supported research into sex differences in opportunities (see this issue's "Boys and Girls Encounter Different Drug Offers, Use Different Refusal Strategies") raises the possibility that gender-specific prevention interventions that focus on drug opportunities could serve to reduce drug use by both males and females," Dr. Wetherington says.

Sources

- Van Etten, M.L., and Anthony, J.C. Comparative epidemiology of initial drug opportunities and transitions to first use: Marijuana, cocaine, hallucinogens and heroin. *Drug and Alcohol Dependence* 54:117-125, 1999.
- Van Etten, M.L.; Neumark, Y.D.; and Anthony, J.C. Male-female differences in the earliest stages of drug involvement. *Addiction* 94(9):1413-1419, 1999. NN

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 3 (August 2000)

Cocaine, Marijuana, and Heroin Abuse Up, Methamphetamine Abuse Down

By Robert Mathias, *NIDA NOTES* Staff Writer

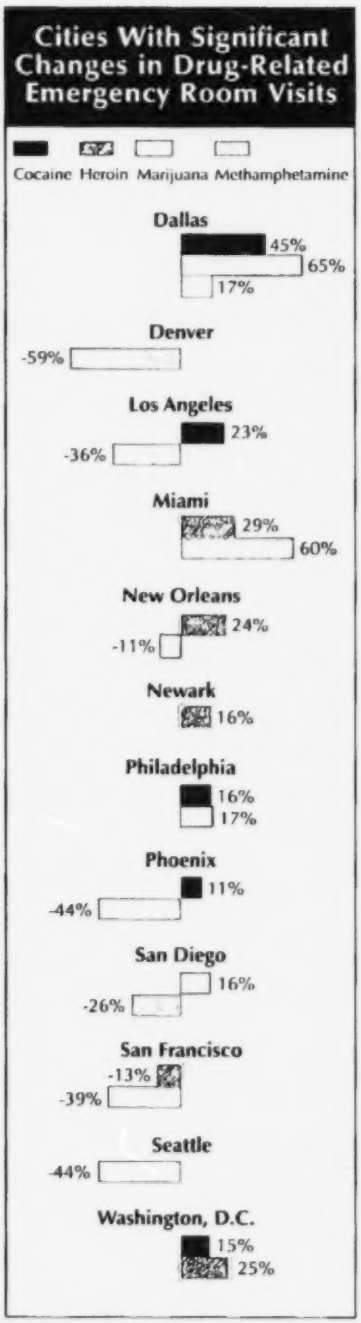
Cocaine abuse indicators increased in many U.S. metropolitan areas during 1998 and the first half of 1999, according to a NIDA-supported network of drug abuse researchers who regularly report data on drug abuse in the United States. The rise follows several years of stable or declining use, the researchers reported at the December 1999 meeting of the Community Epidemiology Work Group (CEWG).

CEWG researchers meet twice a year to report on such drug abuse indicators as drug-related deaths, hospital emergency department (ED) visits, and treatment admissions. Data from 20 cities presented at the December meeting indicate that marijuana and heroin abuse also continued to increase in most areas of the country. However, methamphetamine abuse declined in most cities, including some areas that have been hardest hit by the problem. Highlights from the meeting's advance report are:

Cocaine. Indicators of cocaine abuse increased in half of the 20 CEWG cities, remained stable or mixed in 8, and decreased in 2. Five cities reported significant increases in cocaine-related ED incidents and 9 cities reported large increases in the number of cocaine-related deaths.

Heroin. Heroin abuse indicators increased in 10 CEWG cities, were stable or mixed in 9, and decreased in 1. Heroin abuse and snorting of the drug continued to increase among younger populations, such as college students. These trends were particularly apparent in East Coast cities where pure forms of white powder heroin, which can be snorted, are most available. Heroin-related deaths also increased in many areas of the country.

Marijuana. Seventeen CEWG cities reported increases in problems associated with marijuana abuse. The percentage of drug abusers whose primary drug of abuse was marijuana continued to increase in many cities. Rates of marijuana-related ED visits also continued the consistent, often dramatic, increases shown over the last 6 years. Increases in marijuana-related problems may be tied to increased availability, higher potency, and lower prices for the drug along with perceptions that marijuana abuse is less risky than abuse of other drugs, the report indicates.



Many CEWG cities reported statistically significant increases from 1997 to 1998 in hospital emergency department (ED) visits due to cocaine, heroin, and marijuana use. However, methamphetamine-related ED visits declined sharply in most cities where rates had previously been highest. Source: Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 1998 (July 1999 Update).

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Methamphetamine. Indicators of methamphetamine abuse decreased in West Coast and Southwest areas where abuse of the drug has been a major problem for years. Sharp declines in methamphetamine-related ED visits were reported in 1998 in six CEWG areas. Several areas also reported that methamphetamine treatment admissions, hospital mentions, and deaths continued to decline in the first half of 1999. Researchers cited several possible reasons for these decreases, including initiation of national and community methamphetamine abuse prevention programs and enactment of laws that make it more difficult to obtain the chemicals needed to produce the drug.

Club Drugs. Thirteen cities reported problems with MDMA (ecstasy) abuse. The drug is available at raves and nightclubs in most areas. Ecstasy abuse also is increasing in other settings, such as college campuses. Nine areas reported GHB (gamma-hydroxybutyrate) abuse at raves and clubs. Numerous medical emergencies and several deaths were associated with GHB abuse.

For More Information

The CEWG "Advance Report, Epidemiologic Trends in Drug Abuse, December 1999," is available from NIDA's Web site, www.drugabuse.gov. NN

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 1 (March 2000)

Evidence Accumulates That Long-Term Marijuana Users Experience Withdrawal

By Patrick Zickler, *NIDA NOTES* Staff Writer

Laboratory studies have shown that animals exhibit symptoms of drug withdrawal after cessation of prolonged marijuana administration. Some human studies have also demonstrated withdrawal symptoms such as irritability, stomach pain, aggression, and anxiety after cessation of oral administration of tetrahydrocannabinol (THC), marijuana's principal psychoactive component. Now, NIDA-supported researchers at McLean Hospital in Belmont, Massachusetts, and Columbia University in New York City have shown that individuals who regularly smoke marijuana experience withdrawal symptoms after they stop smoking the drug.

"These studies suggest that in real-world situations abstinence from daily marijuana smoking creates withdrawal symptoms similar to those of other drugs of abuse," says Dr. Jag Khalsa of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "Marijuana smokers may continue to use the drug to prevent the irritability and discomfort they experience when they stop."

Aggression

Dr. Elena Kouri and her colleagues at the Biological Psychiatry Laboratory at McLean Hospital found that long-term heavy marijuana users became more aggressive during abstinence from marijuana than did former or infrequent users. Previous studies of withdrawal symptoms have relied largely on patients' subjective reports of a range of symptoms, Dr. Kouri notes. "We studied measurable changes in one specific symptom—aggression," she says.

The researchers recruited two groups of male and female volunteers: 17 current long-term users of marijuana and a control group of 20 infrequent or former users. Current long-term users were smoking marijuana daily at the time of recruitment and had smoked marijuana at least 5,000 times—the equivalent of smoking once each day for more than 13 years. The infrequent or former users had not smoked more than 50 times in their life and had smoked less than once per month in the past year, or had formerly smoked at least daily but had not smoked more than once per week for the past 3 months.

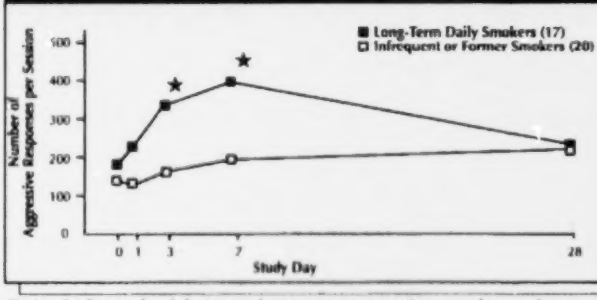
At the beginning of the study, all participants were instructed to refrain from any marijuana use for 28 days. Abstinence was monitored by analysis of daily observed urine sampling. Cigarette smokers were allowed to continue their usual tobacco use.

"The results demonstrate that abstinence is associated with unpleasant behavioral symptoms that may contribute to continued drug use."

Aggression was measured on the first day of the study and after 1, 3, 7, and 28 days of abstinence. To measure aggression, the researchers used a 20-minute computerized test that participants were told would measure motor skills and other physiological characteristics. Participants were told that pressing one button in a certain pattern would add points to their score and that pressing another button would subtract points from the score of their opponent, who could similarly add or subtract points.

In fact, Dr. Kouri says, there was no human opponent; the computer was programed to subtract points randomly in

Abstinence Elicits Aggressive Behavior in Long-Term Marijuana Smokers



During the first weeks of abstinence, long-term current marijuana smokers made more aggressive responses on a computerized game than did infrequent or former smokers. The graph shows the average number of aggressive responses in 17 long-term daily (■) and 20 infrequent or former (□) marijuana smokers. (★ = significantly different from former smokers.)

order to give the illusion of a human opponent. At the end of each session, aggressive responses—those that subtracted from the supposed opponent's points—were compared with nonagressive responses—those that added to the participant's points. Dr. Kouri notes that studies involving parolees with a history of violent behavior have shown a close correlation between performance on this game and actual aggression.

After 1, 3, and 7 days of abstinence, current marijuana users registered significantly more aggressive responses—more than twice as many on days 3 and 7—than the control group. By the 28th day, there was no significant difference between groups. Aggressive behavior was limited to responses in the test situation, Dr. Kouri notes; participants did not display overt hostility. "At this point we do not know exactly how these findings reflect changes in aggressive behavior outside the laboratory," Dr. Kouri says. "But the results demonstrate that abstinence is associated with unpleasant behavioral symptoms that may contribute to continued drug use."

Other Withdrawal Symptoms

Studies at Columbia University in New York City have demonstrated that, in addition to aggression, marijuana smokers experience other withdrawal symptoms such as anxiety, stomach pain, and increased irritability during abstinence from the drug. "These results suggest that dependence may be an important consequence of repeated daily exposure to marijuana," says NIDA-supported researcher Dr. Margaret Haney.

Dr. Haney and her colleagues investigated the effects of abstinence on 12 adult males with an average age of 28 years who, in the laboratory, smoked marijuana with THC concentrations of 3.1 percent or 1.8 percent, or marijuana cigarettes containing no active THC. All participants smoked inactive marijuana during the first 4 days of the study followed by either the high concentration, low concentration, or inactive marijuana on alternating 4-day periods. Three times each day, the participants completed a 50-item checklist that rated physical conditions such as hunger, dizziness, and headache and aspects of their mood, for example, anxiety, talkativeness, friendliness, or depression.

"The withdrawal symptoms are not as dramatic as those associated with withdrawal from opiates or alcohol, but are still significant."

Abstinence from either high- or low-concentration marijuana resulted in reduced hunger, decreased ratings of "friendly" and "content," and increased ratings of "irritability," "stomach pain," and "anxiety." Moreover, Dr. Haney notes, participants receiving high-concentration marijuana rated the drug's effects higher ("good drug effect," "stimulated," "high") on the first day of exposure than on the fourth day, indicating the development of tolerance to THC.

"It appears likely that the onset of the withdrawal symptoms we observed in this study may contribute to maintaining chronic marijuana use," Dr. Haney says. "The withdrawal symptoms are not as dramatic as those associated with withdrawal from opiates or alcohol, but are still significant to the individual marijuana user. These symptoms must be taken into account in order to develop effective treatment programs for marijuana abuse."

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 15, Number 1 (March 2000)

Marijuana-Like Compound in Womb May Influence Early Pregnancy

By Steven Stocker, *NIDA NOTES* Contributing Writer

Ever since scientists began discovering in the early 1990s that marijuana-like compounds are normally produced in various parts of the body, they have been investigating the function of these compounds. Research has suggested that in the brain, the compounds, called endocannabinoids, inhibit pain perception and help to regulate movement. In the spleen and blood, endocannabinoids seem to be partly involved in suppressing inflammation and other responses of the immune system. Now NIDA-funded researchers have discovered that in the female mouse reproductive tract, one of these endocannabinoids, called anandamide, appears to help regulate the early stages of pregnancy.

Dr. Sudhansu K. Dey and his colleagues at the University of Kansas Medical Center in Kansas City, Kansas, have found that the mouse uterus contains the highest anandamide levels yet discovered in any mammalian tissue. At times, parts of the uterus contain anandamide levels that are more than 100 times higher than those in the brain. The researchers have also found that mouse embryos contain cannabinoid receptors—proteins on the cell surfaces that latch on to endocannabinoids in the vicinity—again, at levels that exceed those of the brain.

To find out why the uterus contains anandamide and the embryo contains cannabinoid receptors, the scientists first examined the effects of anandamide on embryo development. When they placed embryos from mice in cell culture, about 90 percent proceeded to the next stage of embryonic development, the blastocyst, which normally implants into the wall of the uterus and eventually becomes a fetus. With the addition of anandamide, only 36 percent proceeded to the blastocyst stage. However, if these embryos were then placed in cell culture without anandamide, most started developing again.

In addition to inhibiting the growth of embryos prior to implantation, anandamide probably also inhibits implantation itself, the researchers found. They determined that administering compounds similar to anandamide prevented blastocysts from implanting in the uterine wall.

Functions of Anandamide

Anandamide may be serving at least three functions before and during implantation, suggests Dr. Dey. First, the compound may be involved in synchronizing the development of the embryo with the preparation of the uterus for receiving it. For example, anandamide secreted into the fluid of the uterine tubes might retard embryo development until the uterus is ready to receive the implanting blastocyst and to sustain it once it has implanted.

Second, anandamide may be involved in embryo selection. "In the mouse, about 15 percent of embryos never implant, and in humans, as many as 60 percent either don't implant or don't survive after implantation," says Dr. Dey. "Perhaps these rejected embryos are inferior in some way, and high anandamide levels in the uterine wall may prevent them from implanting or surviving after implantation."

Finally, Dr. Dey suggests, anandamide may prevent a second blastocyst from implanting nearby one that has already implanted. After the first one implants, the anandamide level in the surrounding area increases again, which prevents other blastocysts from implanting at the same site.

Understanding how anandamide acts in the female reproductive tract may lead to an explanation for some cases of infertility in women, if anandamide is found to exist in the human uterus, suggests Dr. Dey. In these infertile women, excessive uterine levels of anandamide may be disrupting embryo development and implantation, says Dr. Dey.

This research may also lead to the development of new contraceptives that can inhibit embryo development and implantation in the same manner as anandamide. Conversely, it could also lead to the development of fertility agents that act in ways opposite to those of anandamide.

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Research Findings

Volume 14, Number 4 (November 1999)

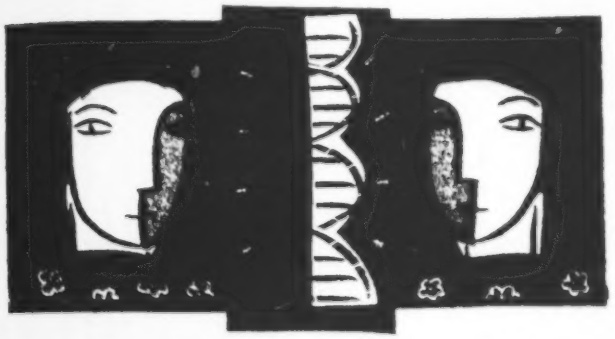
Twin Studies Help Define the Role of Genes in Vulnerability to Drug Abuse

By Patrick Zickler, *NIDA NOTES* Staff Writer

Some individuals who use drugs become drug abusers—they continue taking drugs even though doing so causes serious problems in their lives. Others avoid abuse or addiction. By studying patterns of drug use in pairs of twins, NIDA-supported researchers are beginning to clarify the role that genes play in predisposing individuals to drug abuse.

"Twin studies explore the roles and interrelationship of genetic and environmental risk factors in the development of drug use, abuse, and dependence," says Dr. Naimah Weinberg of NIDA's Division of Epidemiology, Services, and Prevention Research.

In twin studies, researchers interview both members of identical (monozygotic) and fraternal (dizygotic) twin pairs, who typically are exposed to common environmental influences. If genes influence their risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or not abuse drugs. Fraternal twin pairs, on the other hand, are no more similar genetically than non-twin siblings, and so will be less concordant—there will be more pairs in which one twin abuses drugs and the other does not. By comparing the degree of concordance in identical and fraternal twins, researchers can estimate the extent to which genes influence vulnerability to drug abuse.

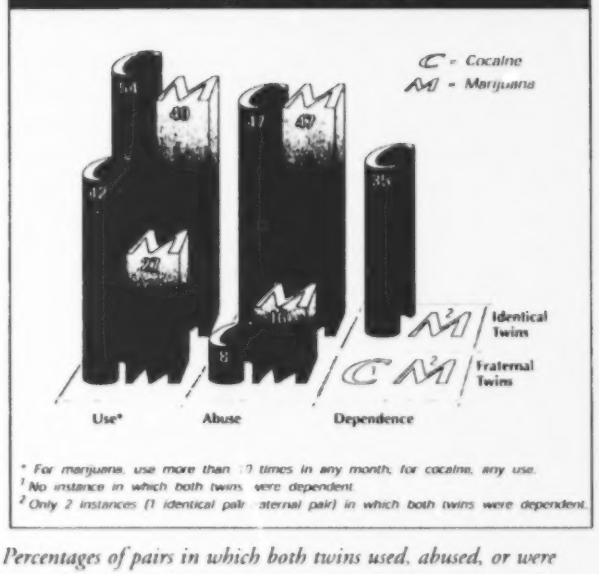


If genes influence the risk for drug abuse, identical twin pairs, who share the same genes, will tend to be concordant—that is, both will abuse drugs or both will not abuse drugs.

Marijuana and Cocaine Abuse Among Female Twins

NIDA-supported researchers Dr. Kenneth Kendler and Dr. Carol Prescott at the Medical College of Virginia in Richmond have examined the patterns of marijuana and cocaine use by female twins and found that genetic factors play a major role in the progression from drug use to abuse and dependence. The researchers interviewed 1,934 twins, ranging in age from 22 to 62, recruited from the Virginia Twin Registry, a database compiled from Commonwealth birth records.

Drug Use, Abuse, and Dependence Among Female Twin Pairs



Percentages of pairs in which both twins used, abused, or were dependent on marijuana or cocaine were higher in identical twins than in fraternal twins.

In the study, drug "use" involved at least one nonprescribed use of a drug; "abuse" was based on the definition provided in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, which includes symptoms such as recurrent use in situations where it presents a physical danger, failure to meet obligations at work or school, or recurrent social or interpersonal problems caused by effects of the drug; and "dependence" was based on the *DSM-IV* definition and included characteristics such as physical symptoms of tolerance or withdrawal, taking larger amounts of the drug or using it over a longer period than intended, or spending large

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amounts of time seeking, obtaining, and recovering from the effects of the drug.

"Our research supports other studies that indicate family and social environmental factors are influential in determining whether an individual begins using these drugs," Dr. Kendler says. "But our findings suggest that the progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors."

In addition, Dr. Kendler says, the study found that concordance rates-both twins using, abusing, or being dependent on drugs-were higher for identical than fraternal twins (see chart). For cocaine use, concordance was 54 percent in identical twins and 42 percent in fraternal twins; for abuse, 47 percent in identical twins and 8 percent in fraternal twins; and for dependence, 35 percent in identical twins and zero for fraternal twins.

"Abuse and dependence are highly heritable," Dr. Kendler says. "For both cocaine and marijuana, genetic factors are responsible for roughly 60 to 80 percent of the differences in abuse and dependence between fraternal and identical twin pairs."

Genetic Risk Factors Differ Among Drugs and Between Males and Females

Dr. Ming Tsuang, a NIDA-supported researcher at Harvard University in Cambridge, Massachusetts, has found that, in males, genetic influences are stronger for abuse of some drugs than for others. Dr. Tsuang and his colleagues studied drug use in 1,874 identical male twin pairs and 1,498 fraternal male twin pairs recruited from the Vietnam Era Twin Registry, a database compiled from Department of Defense records. The average age of participants was 45.

The researchers found evidence to suggest that genetic influences contribute to a common vulnerability for abusing marijuana, sedatives, stimulants, heroin or opiates, and psychedelics. "There is some characteristic of the individual that imparts vulnerability to the abuse of all categories of drugs. Abusing any category of drugs was associated with a marked increase in the probability of abusing every other category of drugs," Dr. Tsuang says. In addition to this shared vulnerability, the researchers found different vulnerabilities for different drugs. "Each category of drugs we looked at, except psychedelics, had unique genetic influences," Dr. Tsuang says. "The genetic influence for abuse was greater for heroin than for any other drug."

NIDA-supported studies involving male and female twins suggest that genetic factors for drug abuse are stronger in males than in females. Dr. Marianne van den Bree and Dr. Roy Pickens of NIDA's Intramural Research Program and their colleagues studied 188 twin pairs in which at least 1 twin was recruited through a drug treatment program. The sample included 56 identical male pairs, 66 fraternal male pairs, 38 identical female pairs, and 28 fraternal female pairs. Participants were interviewed to determine drug use (five times or more) and clinical diagnosis (according to *DSM-IV* criteria) of drug abuse, dependence, or both for sedatives, stimulants, opiates, marijuana, or cocaine. For most drugs, clinical diagnosis of abuse, dependence, or both was more strongly influenced by genetic factors than was drug use. In addition, for most drugs, genetic influences for abuse or dependence were greater for males than for females.

"The progression from the use of cocaine or marijuana to abuse or dependence was due largely to genetic factors."

"For females, genetic influences accounted for 47 percent of the differences between identical and fraternal twins in abuse, dependence, or both for any drug, compared with 79 percent for males," Dr. van den Bree says. The impact of genetic factors also seems to differ for specific drugs, she notes. The researchers found no evidence for genetic influence for opiate or sedative abuse, dependence, or both in females, but in males genetic influences were generally larger than environmental influences.

"The results we see from these twin studies are making important advances in our understanding of the role of genetic influences in drug abuse," observes NIDA's Dr. Weinberg. "Although the studies can't tell us anything about the risk for a particular individual, they are of enormous value in helping define the variations in drug abuse vulnerability in the population."

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 4 (November 1999)

Student Use of Marijuana Linked to Perceptions of Risk

Many American teenagers today do not believe that smoking marijuana is dangerous. That was one of the conclusions of a recent study, by Dr. Jerald G. Bachman and colleagues at the University of Michigan in Ann Arbor, that examined changing attitudes of high school students toward the use of marijuana. The study is based on an extensive review of data from NIDA-supported annual surveys of 8th-, 10th-, and 12th-graders. The surveys, which together make up the ongoing Monitoring the Future project, have collected data on drug use from high school seniors since 1975. Data from 8th- and 10th-graders have been collected since 1991.

The percentage of high school seniors who used marijuana at least once during the past year decreased from 50.8 percent in 1979 to 21.9 percent in 1992, before rising steadily to 37.5 percent in 1998. While use rose, the perception of harm from use declined from 76.5 percent in 1992 to 58.5 percent in 1998. Those who disapproved strongly of regular use dropped from 90.1 percent in 1992 to 81.2 percent in 1998.

Dr. Bachman's group's statistical analysis showed that the simultaneous rise in use and decline in perceived harmfulness during the mid-1990s was more than simple coincidence. To account for this waning concern about the dangers of marijuana, the researchers suggest that the decline in drug use in the 1980s may have led to a "lowering of the guard" of government, schools, mass media, and families. News coverage of drug issues fell substantially in the early 1990s, and fewer antidrug messages were aired during prime-time television programs, the researchers note.

Young people pay close attention to realistically and creatively presented information about the risks of drug use, the researchers suggest. "Presenting this kind of information on the risks and consequences of marijuana use only once does not do the job," says Dr. Bachman. "The message must be repeated regularly so we don't lose students from one year to the next." NN

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Research Findings

Volume 14, Number 3 (September 1999)

Ethnic Identification and Cultural Ties May Help Prevent Drug Use

By Patrick Zickler, *NIDA NOTES* Staff Writer

Among Puerto Ricans, African Americans, and Asians, cultural influences and ethnic identification may significantly influence drug use. Studies conducted by NIDA researchers in New York City suggest that Puerto Rican and African-American adolescents who strongly identify with their communities and cultures are less vulnerable to risk factors for drug use and benefit more from protective factors than do adolescents without this identification. In San Francisco, NIDA-supported research demonstrated different patterns of drug use among different subgroups of the Asian community. These findings suggest that incorporating ethnic and cultural components into drug abuse prevention programs can make these programs more effective.

Adolescents who strongly identify with their communities and cultures are less vulnerable to risk factors for drug use.

In one study, Dr. Judith Brook at the Mount Sinai School of Medicine in New York City examined the extent to which ethnic and cultural factors influenced drug-related behavior in Puerto Rican adolescents. She and her colleagues interviewed 275 males and 280 females aged 16 to 24. The researchers asked the participants to describe the importance in their lives of cultural and ethnic factors such as observation of Hispanic holidays and customs, preference for speaking Spanish or English, feelings of attachment to their ethnic group, ethnic affiliation of their friends, and the value placed on the family. The participants also answered questions designed to assess their personal risk for drug use; these risk factors included the use of drugs by parents or siblings, peer use or tolerance of drug use, perception of the riskiness of drug use, and the availability of illegal drugs in their environment. The participants were categorized into stages of drug use: no reported drug use, used alcohol or tobacco only, used marijuana but no other illicit drug, or used illicit drugs other than or in addition to marijuana.

"Other studies have looked at ethnic identification in isolation, not as an interactive part of a young person's cultural and social context," Dr. Brook says. "We wanted to determine the extent to which ethnic and cultural factors might mitigate risk factors or enhance protective factors and lead to lower stages of drug use. We found that strong ethnic identification acts to offset some risks, resulting in less drug use.

"For example, strong identification with Puerto Rican cultural factors offsets drug risks such as a father's drug use, peer tolerance of drugs, and the availability of drugs. Identification with Puerto Rican friends offsets risks associated with family tolerance for drug use and drug availability," Dr. Brook notes.

Ethnic identification also serves to amplify the effect of protective factors, Dr. Brook says. For example, among participants whose siblings were not drug users, those with a strong Puerto Rican affiliation were significantly more likely to be in a lower stage of drug use than those whose affiliation was weaker.

In a related study that focused on late-adolescent African Americans in New York City, Dr. Brook and her colleagues found a similar interaction between ethnic and cultural identification and drug use. The study involved 627 participants—259 male and 368 female—aged 16 to 25 years.

The researchers found that components of ethnic identity —such as awareness of African-American history and tradition, identification with African-American friends, or participation in African-American cultural activities such as Kwanzaa—interacted with other factors to reduce risk or to enhance protection.

"In isolation, few specific components of ethnic identity play a role as main effects on drug use. Instead, they act in combination with family, personality, or peer influences to blunt the negative impact of risk factors and magnify the positive value of protective factors," Dr. Brook says.

"Together, the research with Puerto Rican and African-American populations points out the importance of incorporating ethnic identity into drug programs," Dr. Brook concludes. "It can be a valuable part of drug prevention programs in communities and can also be applied to individual treatment programs."

Cultural Differences Lead to Different Patterns of Drug Use

In another NIDA-supported study, Dr. Tooru Nemoto and his colleagues at the University of California, San

Francisco, have identified patterns of drug use among Asian drug users that are unique to ethnicity, gender, age group, and immigrant status.

"Large multiracial studies have not distinguished between Asian ethnic groups," Dr. Nemoto says. "The purpose of our study was to describe the patterns of drug use in Chinese, Filipino, and Vietnamese groups and to assess the relationship between cultural factors and drug use among the groups."

The San Francisco study was based on qualitative interviews with 35 Chinese, 31 Filipino, and 26 Vietnamese drug users who were not enrolled in treatment programs. All participants were 18 years or older, with an average age of 32.5, and had used illicit drugs more than three times per week during the preceding 6 months. Overall, immigrants and women represented 66 percent and 36 percent, respectively. However, all Vietnamese were immigrants.

Overall, participants born in the U.S. began using drugs at an earlier age—15 years—than did immigrant Asians—19 years—and were more likely than immigrants to use more than one drug. In general, women started drug use at about the same age as men—about 17.5 years—but ethnic groups showed a varied pattern. Chinese women began earlier—at 15.2 years—than Chinese men—at 18.5 years. Filipino women began using drugs later—at 15.5 years—than Filipino men—at 13.1 years. Vietnamese women in the study started drug use much later—at 27.8 years—than did Vietnamese men—at 19.9 years.

Dr. Nemoto and his colleagues identified differences in drug use among the ethnic groups. Filipino drug users were most likely to have begun drug use with marijuana, while Vietnamese drug users in the study most often started with crack or powder cocaine. Chinese and Vietnamese were twice as likely as Filipinos to be using crack as their current primary drug. Filipinos were four times more likely to be using heroin than were Chinese or Vietnamese. Filipino study participants were more likely than Chinese or Vietnamese to be injecting and less likely to be smoking drugs. There were also significant differences in the characteristics of drug user networks among the ethnic groups. For example, Filipinos were more than twice as likely as Chinese or Vietnamese participants to use drugs in groups that included members of other races or ethnic groups.

"These differences among ethnic groups have important implications for the way we design programs aimed at Asian drug users," Dr. Nemoto says. "Prevention programs should address the common factors among Asian drug users, such as stigma associated with injection drug use, but we should also be careful to incorporate factors that are unique to each target group."

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 1 (April 1999)

MERIT Award Research Helps Reveal Long-term and Developmental Impact of Drug Abuse

By Patrick Zickler, *NIDA NOTES* Staff Writer

Identifying the long-term impact of drugs is crucial to understanding drug abuse and addiction. Chronic use of drugs by adults may have effects that last long after drug use has stopped. In children, exposure to drugs may impair development or contribute to behavioral disorders. But understanding these long-term effects requires well-designed research projects that may last decades. Three recent MERIT Award recipients are carrying out investigations that will provide answers to important questions about the long-term impact of drug use.

Studying the Long-term Consequences of Prenatal Exposure to Marijuana and Cigarettes

Dr. Peter A. Fried

For more than 15 years, Dr. Peter A. Fried, professor of psychology at Carleton University in Ottawa, Canada, has studied mother-child pairs to determine whether prenatal exposure to marijuana, cigarettes, or both affects the development and behavior of children and adolescents. Dr. Fried's MERIT Award will allow him to continue to follow the mother-child pairs as the children develop through their teenage years.

"Dr. Fried's research represents an immense opportunity to obtain previously unattainable information on the long-term consequences of prenatal exposure to marijuana and cigarettes," says Dr. Vincent Smeriglio of NIDA's Center for AIDS and Other Medical Consequences of Drug Abuse. "His research already has made a significant contribution not only to documenting infancy and childhood consequences, but also to exploring possible mechanisms for those consequences."

Dr. Fried's research involves more than 150 children born in the Ottawa area who were exposed before birth to cigarettes, marijuana, or both. Dr. Fried and his colleagues evaluated the children several hours after birth and at 4 days, 7 days, 9 days, 30 days, 6 months, and 1 year. The researchers have evaluated the children annually since their first year to look for developmental and behavioral problems that might be related to prenatal exposure to marijuana or cigarettes. The researchers' findings suggest that marijuana exposure is associated with impaired executive functioning—the ability to make decisions and plan for the future—in the children at 9 to 12 years of age. "The major finding in this study about regular marijuana use during pregnancy is that marijuana can have an impact that may prevent a child from achieving his or her full potential," Dr. Fried says.

Children born to women who smoked cigarettes during pregnancy showed, from infancy through early adolescence, a reduction in auditory-based abilities. From ages 9 to 12, children who were exposed prenatally to tobacco smoke showed a reduction in language scores and poorer performance in tests involving the auditory aspects of reading compared with children born to nonsmokers, with the most heavily exposed children performing worse than those exposed to smaller amounts. "The continuity, over approximately 12 years, of the relationship between auditory and language variables and prenatal exposure to cigarette smoke suggests that these important aspects of behavior are directly affected by maternal smoking," Dr. Fried says.

The MERIT Award will simplify the continuation of this research through a crucial period of the children's development, Dr. Fried notes. "Testing the children at midadolescence is particularly critical. Subtle learning difficulties are most likely to manifest themselves at this stage of development, which involves complex behaviors requiring focused attention and cognitive skills," he says.

Investigating the Effects of Chronic Heavy Marijuana Use

Research has shown that heavy and long-term marijuana users suffer impaired cognitive function during and immediately following periods of marijuana use. But does this impairment last, and for how long, if marijuana use is discontinued?

Dr. Harrison Pope, Jr.

Answers to these questions may come from NIDA-supported research under way at the McLean Hospital Biological Psychiatry Laboratory in Belmont, Massachusetts.

The research is part of the work being done by Dr. Harrison Pope, Jr., who recently received a NIDA MERIT Award to continue his investigations.

Dr. Pope's research focuses on 30- to 54-year-old individuals—including both men and women and representing a range of ethnic and socioeconomic groups—who have smoked marijuana at least 5,000 times. This rate of use is equivalent to having smoked marijuana at least once daily for more than 13 years. The study participants will be given a series of neuropsychological tests during a 28-day period of abstinence—monitored by analysis of observed daily urine collections—from marijuana and other drugs.

Using similar neuropsychological tests, Dr. Pope demonstrated that college-age heavy marijuana users performed more poorly than light users on memory, learning, and attention tests following a 24-hour period of supervised abstinence. "Testing after a longer abstinence period in our new study will allow us to distinguish between prolonged impairment that results from marijuana neurotoxicity and temporary impairment that might simply be the result of marijuana residues or withdrawal effects," Dr. Pope says.

"This unique research will allow us to get a much clearer understanding of the residual effects of chronic heavy marijuana use on brain function," says Dr. Jag Khalsa of NIDA's Clinical Medicine Branch. "Equally important is the MERIT Award's potential for expanding the current research using this rich database."

Looking for Links Between Substance Dependence and Adolescent Conduct Disorder

Dr. Thomas Crowley

Many adolescents who suffer from conduct disorder are also substance dependent, and the two disorders together represent a major health problem for adolescents. Research being conducted by MERIT Award recipient Dr. Thomas Crowley will help clarify the critical relationship between conduct disorders and substance dependence.

Dr. Crowley, at the University of Colorado School of Medicine's Addiction Research and Treatment Service in Denver, has spent more than 20 years treating adolescents referred by criminal justice agencies. "Among the patients diagnosed with conduct disorder, 80 percent are also dependent on marijuana, and more than half are dependent on nicotine," Dr. Crowley says. He found that conduct disorders preceded substance dependence in the majority of the adolescents referred to his program with both conditions. Although many of the patients began their substance use—usually with marijuana or alcohol—as early as age 12, in 75 percent of the patients conduct disorders began even earlier.

"Conduct disorder is a major contributor to substance dependence in these patients, and our work suggests that conduct disorders will coexist with most substance dependence that begins early in adolescence," Dr. Crowley says.

Dr. Crowley says his MERIT-supported research will allow him to investigate more fully the relationship between conduct disorder, attention deficit/hyperactivity disorder, and substance dependence. In addition, Dr. Crowley and his colleagues will examine the possible role of genetic and familial factors in patients suffering from both conditions.

"Antisocial drug dependence—that is, substance dependence combined with conduct disorder or antisocial personality disorder—may be due in part to genetic influences and may need special treatment," Dr. Crowley says. He and other researchers will use behavioral studies and brain imaging to investigate the action of tetrahydrocannabinol, the principal psychoactive component in marijuana, in the brains of adolescents with coexisting conduct disorder and marijuana dependence. "We will identify and quantify the characteristic of comorbidity in these patients and use that information to investigate the underlying behavioral genetics," Dr. Crowley says.

"Dr. Crowley and his research team are one of the very few groups in the country who are addressing this clinical population. Their MERIT-supported studies will be of crucial importance in understanding the psychopathology of conduct disorder, attention deficit/hyperactivity disorder, and antisocial behavior in young adolescents with substance dependence disorder," says NIDA's Dr. Khalsa.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 14, Number 1 (April 1999)

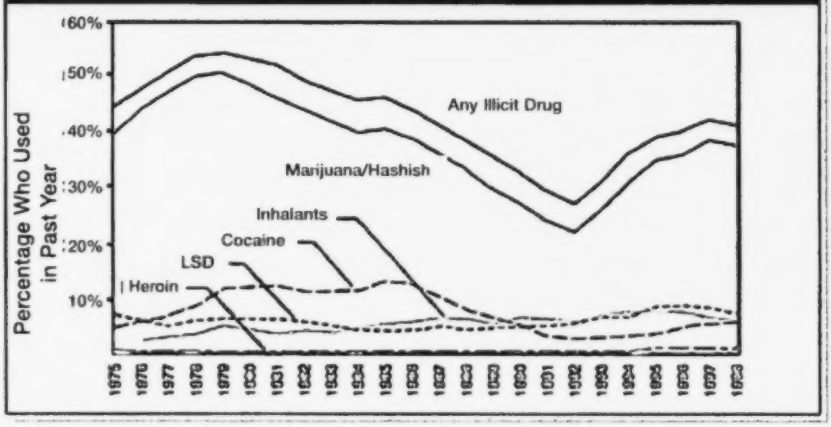
Tracking Trends in Teen Drug Abuse Over the Years

In 1975, shortly after NIDA was established, NIDA's first Monitoring the Future study (MTF) began to collect data on drug use among the Nation's high school seniors. In 1991, 8th- and 10th-grade students were added to the annual study to examine drug use among younger adolescents.

Over the course of its 24-year history, MTF has charted some significant changes in illicit drug use among America's school-aged children. For example, some trends in annual use—use in the past year—include:

- Annual use of any illicit drug by high school seniors peaked at 54.2 percent in 1979, declined to a low of 27.1 percent in 1992, then climbed steadily to 42.4 percent in 1997. Seniors' use of any illicit drug has been stable since then.
- Annual marijuana use among high school seniors crested in 1979 at 50.8 percent, then declined to 21.9 percent in 1992, before rising steadily to 38.5 in 1997. Marijuana use by seniors has remained steady since then.
- Annual cocaine use more than doubled among high school seniors from 5.6 percent in 1975 to 13.1 percent in 1985 then declined sharply to 4.9 percent in 1996. Seniors' cocaine use has been stable since then.
- Heroin use always has been relatively low among school children. However, in recent years, the availability of cheap, high-purity heroin that enables users to get high by snorting the drug rather than injecting it has contributed to heroin use approximately doubling among high school seniors from 0.4 percent in 1991 to 1.0 percent in 1998.

Trends in Past-year Use of Drugs by High School Seniors



The Monitoring the Future study is funded by NIDA and conducted by the University of Michigan's Institute for Social Research.

- Marijuana, cocaine, and heroin use bottomed out in the early 1990s but has since risen among children at all grade levels. MTF figures for 1997 and 1998 suggest this trend toward increased illicit drug use is leveling off and may be in the process of reversing. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 13, Number 6 (March 1999)

Institute Launches Science Education Campaign for Middle Schoolers

By Barbara Cire, *NIDA NOTES* Associate Editor

NIDA has launched a new science education campaign to provide middle school students with information about how drugs work in the brain. "NIDA Goes to School," a compilation of resource materials, is being mailed to science teachers at 18,084 public and private middle schools across the country and 256 Department of Defense schools overseas. The campaign, undertaken in partnership with the National Association of Biology Teachers, was announced in November at the National Leadership Forum of the Community Anti-Drug Coalitions of America in Washington, D.C. In December, at a national press conference about teen drug use, Health and Human Services Secretary Dr. Donna E. Shalala cited the campaign as an effective tool for teaching young people how drugs damage their minds and bodies and helping them to resist drugs.

HHS Secretary Dr. Donna E. Shalala praised the "NIDA Goes to School" campaign at a recent national press conference on teen drug use.

"Science-based education about drug abuse should be a prominent part of the curriculum for all students," says NIDA Director Dr. Alan I. Leshner. "This new initiative provides teachers easily usable, student-oriented materials to help achieve this goal."

The "NIDA Goes to School" kit contains a variety of research-based materials for teachers and students about drugs and how they affect the brain. (See "A Toolbox for Teachers.") In addition, a "NIDA Goes to School" Web site has been established at NIDA's home page on the World Wide Web. Students and teachers can use this interactive Web site to get additional information about drugs of abuse. The site also will serve as a major source of feedback from students, teachers, and parents. As new science education materials are developed, they will be added to the site.

"We are very excited about this project," says Dr. Cathrine Sasek, science education coordinator in NIDA's Office of Science Policy and Communications. "Science teachers want information and resources that they can use in their classes. 'NIDA Goes to School' provides teachers with tools they can use to explain the neurobiology of substance abuse. We also hope that teachers will use NIDA as a source for additional fact-based information about drugs."

Many of the materials are written specifically for students in grades 5 through 9. Seven *Mind Over Matter* magazines feature the adventures of Sara Bellum, a girl who explores the brain's response to particular drugs and introduces key concepts in neuroscience. The series includes magazines on marijuana, opiates, stimulants, hallucinogens, inhalants, steroids, and nicotine. Each magazine unfolds into a poster with a quote from a noted scientist superimposed on a vivid color image of a brain area or neuron. For example, on the reverse side of the magazine on inhalants is a quote from Nobel Prize winner Albert von Szent-GyÖrgyi (1893-1986): "Discovery consists of seeing what everybody has seen and thinking what nobody thought."

Also included in the materials is an interactive CD-ROM that features information on drugs of abuse in a variety of television show formats. Called ATOD-TV—ATOD stands for alcohol, tobacco, and other drugs—the CD-ROM was developed by Dr. Danny Wedding of the Missouri Institute of Mental Health with a NIDA Science Education Drug Abuse Partnership Award. In each ATOD-TV show, human and animated characters play out scenarios that illustrate different aspects of drug abuse and addiction. For example, "Neuronet" is a news program that provides information about the brain and how it is affected by drugs. "The Torn and the Troubled" is a soap opera that challenges myths about drugs and addiction. "Wheels of Misfortune" uses a game-show format to supply statistical information about drug use by different populations. An accompanying teacher's guide suggests student activities and provides a comprehensive list of resources for further information.

A Toolbox For Teachers

The "NIDA Goes to School" kit contains the following publications and materials:

- Seven *Mind Over Matter* magazines and 40-page teacher's guide;
- "ATOD-TV" CD-ROM and 96-page teacher's guide;
- *Marijuana: Facts for Teens*, a 16-page brochure;
- *Marijuana: Facts Parents Need to Know*, a 28-page brochure;
- *Preventing Drug Abuse in Children and Adolescents: A Research-Based Guide*, a 38-page brochure; and
- Twenty NIDA Infofax information sheets on topics of interest to teachers, such as youth drug abuse trends, descriptions of more than 14 commonly abused drugs, and prevention and treatment methods.

"Our goal for this campaign is to enhance science education, increase science literacy, and encourage young people to pursue careers in the sciences," says Dr. Sasek. "By introducing students to the science of drug abuse, we hope to stimulate their interest in neuroscience and substance abuse research."

To Receive This Resource

All materials in the "NIDA Goes to School" kit, with the exception of the ATOD-TV CD-ROM and teacher's guide, are available free from the National Clearinghouse for Alcohol and Drug Information. The materials also can be downloaded from NIDA's home page on the World Wide Web at http://www.nida.nih.gov/. The "NIDA Goes to School" Web site can be accessed from NIDA's home page. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 12, Number 6 (November/December 1997)

Research Must Determine Medical Potential of Marijuana, NIH Expert Panel Concludes

By Robert Mathias, *NIDA NOTES* Staff Writer

A National Institutes of Health (NIH) panel of experts has concluded that critical questions about the therapeutic usefulness of marijuana remain largely unanswered by studies that have been conducted to date. The panel called for NIH to facilitate rigorous, well-designed clinical studies to evaluate marijuana's potential to treat a variety of medical conditions. Such studies must address the many potential short- and long-term hazards of smoked marijuana, the panel stressed.

The panel of eight experts, who have broad experience in clinical studies and therapeutics, expressed their opinions in a 37-page report that NIH issued in August 1997. NIH had convened the experts at a 2-day meeting earlier in the year to consider wide-ranging claims about the therapeutic usefulness of marijuana, particularly smoked marijuana, and the need for and feasibility of additional research. At the meeting, the panel reviewed the published scientific data on the medical use of marijuana and considered comments, including those from patients and advocacy groups.

Under U.S. law, marijuana has been classified in the most restrictive category of controlled substances since 1970. This means that the drug in its usual form has a high potential for abuse and has no commonly accepted medical use in this country. However, advocates for the medical use of smoked marijuana claim it is effective in such areas as reducing nausea associated with cancer chemotherapy, counteracting the wasting syndrome associated with AIDS, and treating glaucoma. An oral form of marijuana's principal active ingredient, delta-9-tetrahydrocannabinol (THC), called dronabinol, is approved as a treatment for nausea and vomiting related to cancer chemotherapy. Dronabinol also is used to stimulate the appetite of AIDS patients.

Any studies of marijuana's medical potential need to consider both the short- and long-term risks associated with smoked marijuana, the panel stressed.

The NIH panel noted that the current debate over using marijuana as a medicine centers on claims that smoked marijuana offers therapeutic advantages over dronabinol and that it has potential to treat other conditions, such as pain and glaucoma. However, little data from clinical trials are available to support or refute these claims, the panel's review showed.

Most previous studies of marijuana's therapeutic potential have used THC in capsule form. Such studies do not answer questions about the potential benefits or risks of smoked marijuana, which has substantially different dose absorption and pharmacological activity from the oral dosage form, the panel noted. In addition, although THC is the principal psychoactive component of the cannabis leaf, other compounds in the leaf may have therapeutic properties, the panel said.

The panel called for more studies to properly evaluate marijuana's medical potential in five areas: analgesia, or pain relief; neurological and movement disorders; nausea and vomiting associated with cancer chemotherapy; glaucoma; and appetite stimulation to counteract weight loss in patients with AIDS or cancer. In addition to dronabinol; effective treatments already are available for many of these indications, the panel noted. For example, a number of medications can treat pain without risking marijuana's adverse effects.

However, even where effective medications exist, marijuana could be studied for its potential to offer relief to patients who do not respond fully to such treatments, the panel stated. Other reasons for studying marijuana's medical potential include determining whether it is useful in treating diseases or conditions for which treatments are not currently available, such as nerve pain caused by disease or tissue injury, and whether it could enhance the therapeutic effects of currently available treatments.

Any studies of marijuana's medical potential need to consider both the short- and long-term risks associated with smoked marijuana, the panel stressed. Among the short-term risks cited by the panel are cardiovascular effects, effects on the lungs, and undesirable mental and behavioral effects. Other concerns would come into play if marijuana were used to treat patients with chronic diseases, such as the possibility that frequent and prolonged marijuana use might significantly impair the functioning

of the body's immune system. Examining that aspect is particularly important for patients who already have compromised immune systems, such as cancer patients undergoing chemotherapy and HIV/AIDS patients, the panel noted.

To address health concerns about using smoked marijuana for longer term therapy, the panel suggested that researchers strive to develop alternative dosage forms for marijuana, such as a smoke-free inhaled delivery system. Such a system could deliver purer forms of THC and related cannabinoids and permit better control of doses, the panel stated.

For More Information

The full text of the expert panel's report on the medical utility of marijuana is available at http://www.nih.gov/news/medmarijuana/MedicalMarijuana.htm NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 12, Number 5 (September/October 1997)

New NIDA Drug Abuse Education Materials for Middle School Students

NIDA has released a new series of drug abuse education materials called *Mind Over Matter*. Designed for students in grades five through nine, the series consists of six full-color glossy magazines that unfold into posters. The package also includes a comprehensive teacher's guide. In each magazine, a girl named Sara Bellum—a play on "cerebellum," a section of the brain that helps control coordination—explores the brain's response to a particular drug and introduces key concepts in neuroscience.

The magazines teach students about the adverse effects of marijuana, opiates, stimulants, hallucinogens, inhalants, and steroids. A seventh in the series, which will discuss nicotine, will be available early in 1998. The magazines are designed to excite students about science in general and neuroscience in particular.

The series uses illustrations and cartoons to provide useful information. Some illustrations show Sara Bellum scuba diving in the depths of the brain, watching drug molecules alter nerve cell activity. The cartoons often depict a nerve cell or body organ performing abnormally under the influence of drugs. For example, a heart playing drums in a rock band loses its rhythm due to cocaine

The posters on the reverse side of each magazine can be seen after the magazine is unfolded. Each 18- by 38-inch poster has a quote from a well-known scientist superimposed over a vivid color photograph of a brain image or neuron. For example, on the back side of the opiates magazine and superimposed over a photograph of neurons in the brain is a quote from Jacob Bronowski, the late British mathematician, which reads, "The essence of science: Ask an impertinent question, and you are on the way to a pertinent answer."

The teacher's guide provides detailed information on the brain and how drugs of abuse affect it. It also lists resources and suggests activities to help students remember the principles discussed in the magazines.

Mind Over Matter is a product of NIDA's Science Education Program, which funds programs to interest children in pursuing careers in science and to increase knowledge about drug abuse and addiction among the general public. The six magazine-posters and the teacher's guide are available free. To order copies, contact the National Clearinghouse for Alcohol and Drug Information, P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686 or (301) 468-2600; TDD number: (800) 487-4889; fax: (301) 468-6433; e-mail: info@health.org. NN

Following are the six magazines and their subjects:

- *The Brain's Response to Marijuana shows how marijuana affects emotions, memory, judgment, balance, and coordination.*
- *The Brain's Response to Opiates discusses how opiates such as heroin act on many places in the brain and spinal cord and how addiction and withdrawal affect neurons.*
- *The Brain's Response to Stimulants demonstrates how cocaine and amphetamines change the way neurons in the brain communicate and disrupt the functioning of the heart and blood vessels.*
- *The Brain's Response to Hallucinogens explains how hallucinogens such as LSD and PCP affect the senses by disrupting the actions of chemical messengers in the brain.*
- *The Brain's Response to Inhalants illustrates how inhalants break down the electrical insulation surrounding many of the body's neurons, making it difficult for them to transmit messages.*
- *The Brain's Response to Steroids describes how anabolic steroids can make people look stronger on the outside and yet cause extensive damage on the inside.*

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 12, Number 4 (July/August 1997)

NIDA-Supported Research Shows. . .

Promising Advances Toward Understanding the Genetic Roots of Addiction

By June R. Wyman, *NIDA NOTES* Staff Writer

This is the second article in a new series, "NIDA-Supported Research Shows," that will appear periodically in NIDA NOTES. The series will explain broad scientific concepts in drug abuse research and describe how NIDA researchers are using these concepts to develop more effective ways to prevent and treat drug abuse and addiction. The first article, "Rate and Duration of Drug Activity Play Major Roles in Drug Abuse, Addiction, and Treatment," appeared in NIDA NOTES, March/April 1997.

At a major scientific meeting, a scientist announced to a spellbound audience that he had identified some of the genes associated with drug abuse. He described the mutations in those genes that lead people to abuse marijuana, heroin, cocaine, and other drugs. His landmark discovery brought scientists a giant step closer to dramatically curbing drug abuse. Although some drug abuse researchers are predicting this tale could come true as early as the next 5 to 10 years, for now it is fiction.

Currently, scientists agree that genetics is involved in drug abuse, but the consensus ends there. Many genes are thought to act together to make someone more likely to abuse drugs. But exactly which genes those are and what they do are the subject of a lively scientific debate. Further, since drug addiction appears to be the product of both heredity and environment, the roles of the two are hard to separate.

At NIDA, a Genetics Workgroup is trying to sort out these issues. The group's mission is to assess the state of the science, identify research gaps, and decide what studies are needed to untangle the genetic roots of addiction. Its members consult with experts from around the country to get advice on what directions NIDA should take, according to Dr. Jonathan Pollock of NIDA's Division of Basic Research, who chairs the group.

Meanwhile, amid the debate, new scientific information is emerging, giving scientists leads that may generate new strategies for drug abuse prevention and treatment.

Family Resemblances

Whether or not someone feels good after smoking marijuana is strongly influenced by heredity, report NIDA-funded grantees from Harvard Medical School. Their conclusion comes from a study of 352 pairs of identical male twins and 255 pairs of fraternal male twins, all of whom had smoked marijuana more than five times in their lives. Identical twins have exactly the same genes, while in fraternal twins about half the genes are identical.

Dr. Ming Tsuang, Dr. Michael Lyons, and their colleagues compared the identical twins' answers with the fraternal twins' answers to a set of questions about how good or bad they felt after smoking marijuana. The identical twins' answers were significantly more alike than those of the fraternal twins. The researchers interpret their data to mean that genetic factors have a significant impact on whether someone will enjoy marijuana.

It is this kind of research that begins the search for drug abuse genes. Although studies of twins and families cannot pinpoint specific genes related to drug addiction, they can look closely at people who share a drug abuse disorder and a common genetic makeup. "Twin studies are promising because they ask exactly what is heritable," says Dr. Harold Gordon of NIDA's Division of Clinical and Services Research. Then, using blood samples, molecular biologists can examine these individuals' genetic material, or DNA, to locate shared genetic characteristics, he says.

To advance such work, NIDA has expanded funding to epidemiologists who work with large numbers of twins or families but have not previously studied addiction to drugs other than nicotine and alcohol. For example, Dr. Kenneth Kendler of Virginia Commonwealth University in Richmond has been studying the genetic basis of nicotine dependence in a large database of twins and siblings in Virginia. NIDA's support has allowed him to launch an epidemiologic survey of those twins that will flag vulnerability to a wide range of drugs including nicotine, cocaine, barbiturates, opiates, inhalants, and marijuana. To measure gender differences, he is doing separate analyses of female/female twins and male/male twins.

Dr. Roy Pickens of NIDA's Division of Intramural Research (DIR) in Baltimore, with colleagues at Johns Hopkins University in Baltimore and the University of Minnesota in Minneapolis, also has been studying twins. Their study looked at same-sex twins, half identical and half fraternal, with coexisting, or comorbid, drug addiction, alcohol abuse, and/or mental health problems. The researchers' analyses suggest that common genetic factors

are involved in drug and alcohol abuse and certain psychological disorders in men. They speculate that this may account for some of the comorbidity among these disorders. Genetic influences were not identified in women, probably because there were not enough women in the study, says Dr. Pickens.

Identical twins have exactly the same genes. Scientists study twins to look for the genetic basis of disorders such as drug abuse.

Likely Candidate Genes

Meanwhile, geneticists are homing in on particular drug abuse genes—a daunting task, given that humans have around 100,000 genes and, of those, more than 40,000 may be expressed in the brain, where drugs of abuse act. Still, many scientists are optimistic. "We've known for a long time that genetics is an important part of an individual's response to drugs of abuse," says Dr. John Crabbe, a NIDA grantee at Oregon Health Sciences University in Portland. "What we're able to do now is get our hands on specific candidate genes."

Of particular interest are genes that control the brain chemical dopamine, which is associated with movement and pleasure, including pleasure from drug use. "Genes in the dopamine circuit are likely candidates, and most of these have been examined at least to some degree," says Dr. George Uhl, chief of DIR's Molecular Neurobiology Branch. This work is being done in mice, which have critical genetic similarities to humans. Also, scientists know more about the genetic makeup of mice than that of any other mammal except humans.

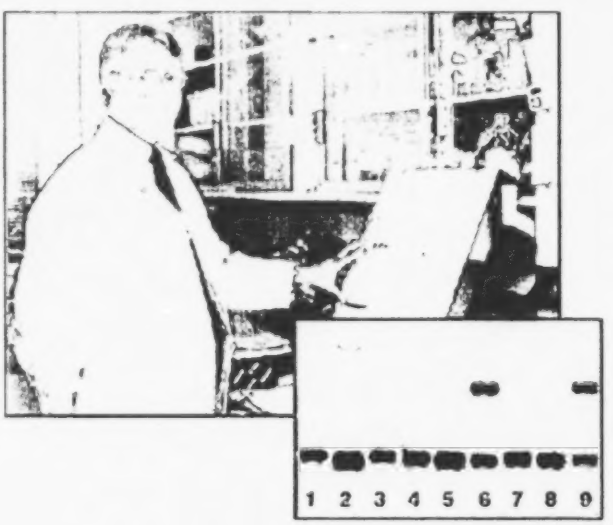
One approach to studying the genes that may influence drug responses is to remove, or "knock out," a candidate gene in mice and see what happens. For example, DIR Scientific Director Dr. Barry Hoffer and scientists from two Swedish laboratories recently used genetic engineering techniques to knock out the gene for a protein called Nurr1. The brains of these mice lacked the two major groups of dopamine neurons and, thus, could not produce any dopamine.

The scientists conclude that in mice Nurr1 is critical for normal development of dopamine-containing nerve cells, and they speculate that development of those cells may be abnormal in people who are vulnerable to substance abuse. "These people may be abusing drugs in an attempt to counteract the deficiency," says Dr. Hoffer, who did the study with scientists from the Karolinska Institute and the Ludwig Institute for Cancer Research, both in Stockholm. "Medications could be developed that interact with Nurr1 and thus regulate dopamine levels in the brain," Dr. Hoffer speculates. "These medications could be useful in treating an underlying disorder that might make some people more likely to abuse drugs."

Another approach to studying the genetics of addiction is to study responses to drugs in genetically identical strains of mice. At Oregon Health Sciences University and the Portland Veteran's Administration Medical Center, Dr. Crabbe and Dr. John K. Belknap have studied more than 25 strains of these inbred mice. "There are big differences among strains in whether they self-administer different drugs," Dr. Crabbe observes. For example, a strain called DBA/2 refuses most drugs of abuse, while C57BL/6 mice seem to like almost everything, including alcohol, morphine, cocaine, phenobarbital, and diazepam. Other inbred strains fall between these extremes. "This work shows that specific genes cause animals to like particular drugs, so that vulnerability to drug abuse is partly under genetic control," says NIDA's Dr. Pollock.

So the evidence from animal studies is compelling. But finding equally strong evidence in humans for a genetic influence on drug addiction has proved trickier. Although a number of genes have been implicated, none has been clearly linked to drug addiction.

At DIR, Dr. David Vandenbergh, Dr. Uhl, and their coinvestigators are looking for genes that may be involved in drug abuse by comparing DNA from drug abusers to that of



NIDA's Dr. George Uhl examines a gene that codes for a type of dopamine receptor—a molecule to which the brain chemical dopamine attaches itself. The inset shows a particular gene from nine different people; each column represents one person. Columns 6 and 9, which have two dark blots—are genetically different from the others. Researchers are trying to determine whether genetic differences such as these relate to drug abuse.

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people who do not abuse drugs. So far the strongest candidate is a variant of a gene that tells the body to produce an enzyme called COMT (catechol-o-methyltransferase). Widespread throughout the body, this enzyme helps break down and inactivate dopamine and related substances. COMT occurs in two genetically determined forms: low activity and high activity. "We found that the high-activity forms of the gene and the enzyme are found more often in drug abusers," Dr. Vandenbergh says. If further work confirms this finding, then drugs that lower COMT activity could be tested as treatments for drug addiction, he says.

Gene Hunters

What will it take to locate the particular genes involved in human drug addiction? Some scientists think that the best bet is what scientists call a genome-wide scan. This method, which was recently used to identify the genetic defect for Parkinson's disease, entails several steps:

- find families with high rates of the disorder;
- analyze blood samples from these people to locate the genetic markers, or stretches of DNA, that family members with the disorder seem to share that are different from those who do not have the disorder;
- scan all known human genes using sources such as the National Institutes of Health's Human Genome Project, and try to find some connection—for example, a gene on the chromosome that is known to regulate dopamine levels; and
- go back to the blood samples to look for shared mutations in those genes.

But applying this method to drug addiction will not be straightforward. "What should we look at? Drug abuse per se? Sensation seeking? Specific biological markers? We really don't know," says Dr. Gordon.

"These genes could operate in many ways. They might make you seek sensations or make it hard to withdraw once you start abusing drugs or make you get higher than other people. Or maybe you need all of these to become a drug abuser," says Dr. Pickens.

Dr. Crabbe in Portland is one of those researchers who thinks that identifying some of the genes involved in drug abuse and addiction is in sight. "That's the big thing that will happen in this field in the next 5 to 10 years. We'll turn the theory that genes influence addiction into the identification of specific genes," he predicts.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 12, Number 1 (January/February 1997)

Smoking Any Substance Raises Risk of Lung Infections

By Michael D. Mueller, *NIDA NOTES* Staff Writer

Smoking any substance—tobacco, marijuana, or "crack," a smokable form of cocaine—increases a smoker's risk of developing bacterial pneumonia and other infections of the lungs, according to the findings of drug abuse, smoking and health, and AIDS researchers.

Although some drugs seem to have specific damaging effects when smoked, smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease, according to NIDA-funded studies. Damaging the lung's cilia, the respiratory system's first line of defense, can have severe consequences for people with weak immune systems, the studies note.

A NIDA workshop held in August 1995 examined current research at that time on the cardio-pulmonary complications of crack cocaine use. In a report summarizing the major findings presented at the workshop, Dr. Pushpa V. Thadani, a pharmacologist in NIDA's Division of Basic Research, notes that smoking cocaine appears to weaken the crack smoker's natural resistance to infection in the lungs.

Smoking anything appears to damage or paralyze the cilia, the hair-like projections in the lungs that sweep out microbes and other matter that can cause disease.

"Pulmonary alveolar macrophages—cells that protect the lungs from infectious agents—are exposed to the highest concentrations of cocaine," says Dr. Thadani. NIDA-funded studies show that alveolar macrophages from crack cocaine smokers are less active than are alveolar macrophages from nonsmokers in destroying Staphylococcus aureus, a common cause of bacterial lung infection. Preliminary findings also indicate that alveolar macrophages of cocaine smokers are more susceptible to HIV-related infections than are alveolar macrophages of people who do not smoke cocaine.

"Much remains unknown about the effects of crack smoking on the alveolar macrophages and other cells of defense in the lungs," says Dr. Thadani. "However, it appears that there are profound effects, and this needs to be further explored," she says.

Dr. Donald P. Tashkin, a professor of medicine at the University of California at Los Angeles School of Medicine, and his colleagues recently examined the effects that habitual smoking of tobacco, marijuana, and/or cocaine has on the lining of the lung's air passages. The NIDA-funded study included 53 nonsmokers, 14 smokers of crack cocaine only, 40 smokers of marijuana only, and 31 regular tobacco smokers. In addition, there were 16 smokers of both cocaine and marijuana, 12 smokers of cocaine and tobacco, and 44 smokers of both marijuana and tobacco. Thirty-one patients smoked all three substances.

The researchers found that smoking either marijuana or tobacco produces significant damage to the cilia in the lining of the airways. Among smokers of both marijuana and tobacco, it appears that the effects of marijuana add to the effects of tobacco, and vice versa. "The damage to the ciliated cells in the lining of the airways caused by smoking tobacco, and/or marijuana weakens the ability of the lungs to remove inhaled particles, making the lungs more vulnerable to infection," says Dr. Tashkin.

Cocaine smokers had fewer significant abnormalities than marijuana or tobacco smokers did—but more abnormalities than were detected among nonsmokers, Dr. Tashkin says. Among people who smoke both tobacco and cocaine, cocaine smoking appears to produce injury to the mucosal lining of the airways beyond that caused by smoking tobacco alone.

A NIDA-supported study by Dr. Waleska T. Caiaffa and her colleagues at Johns Hopkins University in Baltimore compared the medical records of 40 HIV-positive injecting drug users (IDUs) who had suffered from one bout of bacterial pneumonia with those of 197 HIV-positive IDUs with no history of bacterial pneumonia. The study found that HIV-positive IDUs who smoked illicit drugs were almost twice as likely to develop bacterial pneumonia as were their counterparts who did not smoke illicit drugs. This association was independent of age, degree to which the natural immune system had been suppressed, and cigarette smoking. Among the 77 HIV-positive IDUs who reported smoking drugs, 87.9 percent indicated that they had smoked marijuana, 25.9 percent said that they had used cocaine, and 9.1 percent admitted smoking crack.

Smoking is a serious issue among AIDS patients, according to several NIDA-supported studies. The health effects of smoking illicit drugs are above and beyond those caused by smoking cigarettes, the studies note. People with AIDS often die of pneumonia and other lung problems, and smoking tobacco and/or illicit drugs increases the risks for these diseases.

"The effect that smoking has on the lungs is more serious than most people realize. Smoking anything is bad for your health, especially if your immune system has been weakened," says Dr. Tashkin.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 11, Number 3 (May/June 1996)

Studies Show Cognitive Impairments Linger in Heavy Marijuana Users

By Robert Mathias, *NIDA NOTES* Staff Writer

Students who smoke marijuana heavily may be limiting their ability to learn, according to a NIDA-funded study. The study found that college students who used marijuana regularly had impaired skills related to attention, memory, and learning 24 hours after they had last used the drug. The finding supports the results of previous NIDA-funded research that reported that adults who were chronic heavy marijuana users showed residual impairment in cognitive abilities a day after they had last used marijuana.

Using the Wisconsin Card Sorting Test, shown here, Dr. Harrison Pope, Jr. (left) found that 24 hours after they stopped using the drug, heavy marijuana smokers made a greater number of errors than light users made in sorting cards into different categories.

"Now we know that for students who smoke marijuana heavily, the ability to learn is affected not just while they are high, but for at least a day after," says NIDA Director Dr. Alan I. Leshner. Together with other NIDA-funded research that has shown a marked increase in daily marijuana use among young people in recent years, this finding underlines the importance of the Marijuana Use Prevention Initiative launched by Health and Human Services Secretary Dr. Donna Shalala last year, Dr. Leshner says. NIDA is playing a leading role in the initiative by providing science-based information to educate the public about the consequences of marijuana use. (For more information, "Marijuana Conference Advances HHS Secretary's Marijuana Initiative," V10-6 Novevember/December 1995, and "Facts About Marijuana and Marijuana Use," V11-1, March/April 1996.)

Regular heavy marijuana use compromises the ability to learn and remember information primarily by impairing the ability to focus, sustain, and shift attention, says Dr. Harrison Pope, Jr., of McLean Hospital in Belmont, Massachusetts, who directed the recent study. Noting that the actual ability to recall information remains relatively unaffected, Dr. Pope says, "If you could get heavy users to learn an item, then they could remember it; the problem was getting them to learn it in the first place."

In the study conducted among college students, Dr. Pope and Dr. Deborah Yurgelun-Todd, also of McLean Hospital, tested the cognitive functioning of 65 heavy cannabis users, most of whom had smoked marijuana at least 27 out of the previous 30 days. The researchers compared the heavy users' cognitive functioning to that of a comparison group of 64 light users, most of whom had smoked marijuana on no more than 3 of the previous 30 days. Heavy users ranged in age from 18 to 24 years and light users from 18 to 28 years. The two groups were similar demographically and had comparable numbers of men and women. Subjects in both groups had smoked marijuana for at least 2 years, and none had smoked regularly for more than a decade.

To ensure that the subjects did not smoke marijuana or use other illicit drugs or alcohol during the study, researchers monitored them for 19 to 24 hours. Then the subjects performed a battery of standard tests designed to assess their ability to pay attention, learn, and recall new information. The tests indicated that heavy marijuana users had more difficulty than light users in sustaining and shifting attention and hence in registering, organizing, and using information. Heavy users exhibited these cognitive deficits by being less able than light users were to learn word lists; by making a greater number of errors in sorting cards by different characteristics, such as by color or shape; and by making more errors when the rules for sorting the cards were changed without warning. Men in the heavy users group showed somewhat greater impairment than women in the same group.

While the residual cognitive impairments detected in the study were not severe, they could be significant in the day-to-day life of chronic users, Dr. Pope says. The diminished ability to pay attention and decreased mental flexibility exhibited in these tests may cause chronic marijuana users

important difficulties in adapting to intellectual and interpersonal tasks, he says.

"This is a fairly definitive study because it was methodologically sound and controlled for a wide number of factors, including the possible confounding effects of alcohol and other drug use," says Dr. Jagjitsing Khalsa of NIDA's Division of Clinical and Services Research.

Previous studies have produced mixed findings about the residual effects of heavy marijuana use on neuropsychological performance, notes Dr. Khalsa. Methodological problems such as ambiguous terminology, failing to take into account cognitive differences in study participants prior to initiation of marijuana use, and failing to note the possible effect of alcohol and other drugs have raised questions about the results of many of these studies. (For more information about methodological issues, see the Pope, Gruber, and Yurgelun-Todd article listed below.)

The study joins a growing body of research that indicates protracted cognitive impairment among heavy marijuana users.

The study by Dr. Pope and Dr. Yurgelun-Todd joins a growing body of well-controlled and well-designed studies that indicate protracted cognitive impairment among heavy marijuana users, says Dr. Khalsa. For example, in 1993, Dr. Robert Block of the University of Iowa College of Medicine compared adult heavy marijuana users and nonusers ranging in age from 18 to 42 years who had been matched on the basis of their intellectual functioning before the onset of drug use. Subjects who used marijuana frequently—7 or more times weekly for at least 2 years—showed deficits in mathematical skills and verbal expression and selective impairments in memory retrieval processes, the study reported. Although the two studies used different neuropsychological tests, "in general, both studies showed some impairments in cognitive abilities among heavy marijuana users," Dr. Block says.

It remains unclear whether marijuana's short-term residual cognitive impairments are due either to a residue of the drug that remains in the brain after marijuana's acute effects have dissipated, to a withdrawal effect from abrupt discontinuation of the drug, or to a neurotoxic effect of the drug on brain structure or function. Research has yet to demonstrate conclusively that chronic heavy marijuana use results in cognitive deficits that persist after a prolonged period of abstinence. However, NIDA-supported animal studies do show structural damage to the hippocampus, a structure critical in learning and memory, from the principal psychoactive ingredient in marijuana.

To help answer these and other questions about the long-term effects of marijuana, both Dr. Pope and Dr. Block plan followup studies to examine the effects of chronic heavy marijuana use on cognition and brain function after longer periods of abstinence. Dr. Block proposes to use neuroimaging techniques to look at heavy users' brains while they perform cognitive tasks to determine whether brain function or structure is altered after abstinence from marijuana for a minimum of 30 hours. Dr. Pope is planning a study to determine if cognitive impairments persist in long-time heavy marijuana users for up to 28 days after they have stopped using marijuana.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 11, Number 1 (January/February 1996)

Marijuana Impairs Driving-Related Skills and Workplace Performance

By Robert Mathias, *NIDA NOTES* Staff Writer

Marijuana use impairs driving-related functions and is linked to a pattern of behaviors that leads to poor job performance, according to two NIDA-supported studies on the effects of marijuana on human performance. Findings from the studies were presented at NIDA's first National Conference on Marijuana Use.

"Driving and marijuana do not mix; that's the bottom line," said Dr. Stephen J. Heishman, a research psychologist in the Clinical Pharmacology Branch of NIDA's Division of Intramural Research. Figures from previous studies of automobile accident victims show that from 6 to 12 percent of nonfatally injured drivers and 4 to 16 percent of fatally injured drivers had tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana, in their bloodstream, Dr. Heishman said. One study showed that 32 percent of drivers in a shock trauma unit in Baltimore had marijuana in their bloodstream, he noted. However, in most of these studies, the majority of subjects who tested positive for THC also tested positive for alcohol, making it difficult to single out THC's effect on driving.

In a laboratory study at NIDA's Addiction Research Center in Baltimore that controlled for alcohol's confounding effect, Dr. Heishman tested marijuana's effects on the functional components of driving. Study subjects smoked a marijuana cigarette, waited 10 minutes, then smoked another cigarette. Both cigarettes contained either 0, 1.8, or 3.6 percent THC. Twenty minutes after smoking the cigarettes, the subjects were given a standard sobriety test similar to a roadside sobriety test. The test showed that marijuana significantly impaired their ability to stand on one leg for 30 seconds or touch their finger to their nose. As the dose of THC increased, the subjects swayed more, raised their arms, and had to put their feet down in an attempt to maintain their balance. Subjects also committed 2.5 times more errors when they attempted to touch their nose with their finger.

The data from these laboratory studies show that marijuana impairs balance and coordination—functional components important to driving—in a dose-related way, said Dr. Heishman. These effects may be related to reported marijuana-induced impairment of automobile driving, he stated.

Highway and urban driving studies conducted in the Netherlands show less impact on actual driving. However, these driving studies used very low doses of marijuana for safety reasons, Dr. Heishman said. Future research using appropriate safety measures should test the effect of higher doses of marijuana on driving as well as the combined effect of marijuana and alcohol on driving, he concluded.

At NIDA's National Conference on Marijuana Use, Dr. Stephen Heishman presented data from laboratory studies showing that marijuana impairs functions important to driving.

In another study, Dr. Wayne Lehman of Texas Christian University looked at how marijuana affects job performance. A series of surveys he conducted among 4,600 municipal employees in four cities in the Southwest indicated that 8 percent of employees had smoked marijuana in the past year, and a large percentage of these users had smoked marijuana in the past month, Dr. Lehman said.

"Employees who report marijuana use are different from nonusers," said Dr. Lehman. They are much more likely than nonusers to have arrest histories, low self-esteem, high rates of depression, and friends who are deviant. Many marijuana smokers also have alcohol-related problems. One-third of marijuana users in the surveys reported they drank frequently, one-half said they got drunk, and 60 percent reported a problem with alcohol use, according to Dr. Lehman.

This behavioral pattern in the personal backgrounds of marijuana-smoking employees was associated with negative attitudes toward work and job performance, Dr. Lehman said. The surveys found that marijuana users were less likely than nonusers to commit to the organization, had less faith in management, and experienced low job satisfaction. These workers reported more absenteeism, tardiness, accidents, workers' compensation claims, and job turnover than workers who had not used marijuana. They were also more likely to report to work with a hangover, miss work because of a hangover, and be drunk or use drugs at work.

These data indicate that marijuana use is strongly associated with problematic alcohol use and a pattern of general deviance that leads to impaired behaviors and poor workplace performance, Dr. Lehman concluded. NN

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Research Findings
Volume 10, Number 6 (November/December 1995)

NIDA Conference Advances HHS Secretary's Marijuana Initiative

Approximately 570 marijuana researchers, treatment and prevention services providers, and educators met in Arlington, Virginia, July 19-20, to learn about new marijuana research findings. The occasion was NIDA's Conference on Marijuana Use: Prevention, Treatment, and Research, the first national conference ever held on the topic.

The conference was a key component of the Marijuana Use Prevention Initiative, a multifaceted campaign being spearheaded by the Department of Health and Human Services. The conference furthered the Initiative's core objective of using science-based information to educate the public about the consequences of marijuana use. (For more about the Initiative, see "HHS Secretary Sends Marijuana Information to the Nation's Schools," and "NIDA Expands Its Marijuana Research Agenda.")

NIDA's 2-day Conference on Marijuana Use drew some 570 researchers, treatment and prevention services providers, and educators from across the Nation to hear the latest research findings on marijuana.

"The marijuana issue is about the costs to society of drug-related auto wrecks, accidents, property damage, truancy and school failure, on-the-job mishaps, and lost productivity," Health and Human Services Secretary Dr. Donna E. Shalala told conference participants. "At the core of our agenda must be a clear and consistent message: Marijuana is illegal, dangerous, unhealthy, and wrong."

During the 2-day conference, more than 60 speakers discussed marijuana topics ranging from current patterns of use and perceptions of risk to physical and behavioral effects and prevention and treatment approaches. Among the research results presented:

- Dr. Billy Martin of the Medical College of Virginia at Virginia Commonwealth University released new research showing that marijuana produces drug dependency in animals (see "Marijuana Antagonist Reveals Evidence of THC Dependence in Rats").

NIDA Expands Its Marijuana Research Agenda

In conjunction with the Marijuana Use Prevention Initiative, NIDA has expanded its marijuana research agenda. Its new Marijuana/Cannabis Abuse Research Program Announcement (PA 95-076) is encouraging research on the entire spectrum of marijuana abuse. Research areas of interest include etiology, epidemiology, prevention, treatment, and clinical and basic science.

Receipt dates for grant applications are February 1, June 1, and October 1 of each year. For further information on programmatic issues, contact

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Copies of program announcements and information regarding fiscal issues may be obtained from

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From NIDA NOTES, November/December, 1995

- Dr. Donald Tashkin of the University of California at Los Angeles reported his findings on the pulmonary consequences of habitual marijuana use, which include symptoms of chronic bronchitis, an increased frequency of acute chest illnesses, a heightened risk of pulmonary infection, and an apparently increased risk of disease in both the upper airway and the lungs.
- Preliminary findings presented by Dr. Peter Fried of Carleton University in Ottawa suggest that, in 9- to 12-year-olds, prenatal marijuana exposure is associated with impaired executive function, the intellectual ability that involves decisionmaking and planning.
- Dr. Stephen Heishman of NIDA's Division of Intramural Research discussed his recent study, which showed that marijuana significantly impaired performance in standardized sobriety tests conducted in controlled laboratory conditions.
- Dr. Judith Brook at the Mt. Sinai School of Medicine in New York City presented findings from a multigenerational study showing certain factors associated with marijuana use among young people. Study results indicate that children who are aggressive and have a distant relationship with their parents are more likely than other children to use marijuana as young adults, and that adolescents at risk for marijuana use exhibit rebelliousness, poor school achievement, and difficulty in family relationships.

Conference proceedings and audio cassettes of conference sessions are available. Proceedings may be ordered from the National Clearinghouse for Alcohol and Drug Information (NCADI), P.O. Box 2345, Rockville, MD 20847-2345, (800) 729-6686 or (301) 468-2600. Information on ordering audio cassettes. NN

HHS Secretary Sends Marijuana Information to the Nation's Schools

With the distribution of NIDA developed materials on marijuana to 16,000 U.S. school districts in October, the national Marijuana Use Prevention Initiative delivered a new wave of science based information to the Nation's school-aged children and their parents.

The materials were accompanied by a letter from Health and Human Services Secretary Dr. Donna E. Shalala, who launched the Initiative at the end of last year in response to disturbing increases in teenage use of marijuana reported in NIDA's 1994 Monitoring the Future survey.

The school districts received a 13 minute informational video for parents-"Marijuana: What Can Parents Do?"

Two question-and-answer brochures accompanied the video: "Marijuana: Facts for Teens" and "Marijuana: Facts Parents Need to Know."

In addition, full-color posters bearing the messages "Drugs Have No Place in a Healthy Life!" and "Marijuana Can Mess You Up!" were distributed as supplements to "My Weekly Reader" and a number of other educational periodicals used in the school systems.

In developing the Marijuana Use Prevention Initiative, NIDA collaborated with the Center for Substance Abuse Prevention and the Center for Substance Abuse Treatment, both agencies of the Substance Abuse and Mental Health Services Administration, and the Partnership for a Drug-Free America, a communications industry coalition to reduce the demand for illicit drugs.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 10, Number 6 (November/December 1995)

Marijuana Antagonist Reveals Evidence of THC Dependence in Rats

By Neil Swan, *NIDA NOTES* Contributing Writer

For the first time, researchers have demonstrated that marijuana may cause drug dependency in animals. This finding was made possible by the recent development of a potent marijuana antagonist—an agent that blocks many effects of the drug. The marijuana antagonist appears to act like an on-off switch, allowing researchers to control the effects of withdrawal from delta-9-tetrahydrocannabinol (THC), the principal psychoactive ingredient of marijuana.

Dr. Billy Martin, a NIDA-funded marijuana researcher at Virginia Commonwealth University's Medical College of Virginia, who conducted one of two initial studies, presented his findings at NIDA's National Conference on Marijuana Use: Prevention, Treatment, and Research last summer. During his research, rats were exposed to THC for 4 days, then given a dose of the THC antagonist SR 141716A, which was developed by French scientists last year. The rats immediately and "dramatically" exhibited classic rodent behavioral withdrawal symptoms, indicating that they were dependent on THC, Dr. Martin said.

Within 10 minutes after administration of the marijuana antagonist, the rats exhibited behavior that included "wet-dog shakes" and facial rubbing, which constitute "definite evidence of withdrawal" from the effects of THC, said Dr. Martin. This behavior mimics long-observed opiate withdrawal symptoms in rodents.

The shakes and rubbing were so striking and frequent that they could be quantified by trained observers. Other, less frequent withdrawal-like behaviors included head shakes, biting, drooping eyelids, retropulsion (backing away), ear twitching, chewing, licking, and arching the back, Dr. Martin said.

The wet-dog shakes were dose-dependent, meaning they became more pronounced as dose levels of the antagonist were increased in the THC-exposed animals.

Dr. Martin acknowledged that such behavior is not like any marijuana withdrawal syndrome in humans.

"The fact that people do seek treatment for marijuana dependence is evidence of marijuana withdrawal in humans, but, even among those seeking treatment, we do not see dramatic withdrawal symptoms," said Dr. Martin.

Dr. Billy Martin found that when rats that are adminstered the main psychoactive ingredient in marijuana are then given doses of a compound that blocks the action of this ingredient, the rats "dramatically" exhibit classic rodent withdrawal symptoms.

"That's because the withdrawal process in humans is so long and drawn out, evidenced chiefly by mild distress or anxiety. But with the rats, using SR 141716A as an effective antagonist, we compress and accentuate that withdrawal process.

"The challenge for us now is to use these animal data to design human studies-to determine how small a dose of THC is needed to become dependent on marijuana," said Dr. Martin.

Dr. Martin, senior investigator Dr. Mario D. Aceto, and colleagues at the Department of Pharmacology and Toxicology of Virginia Commonwealth University have published the results of their research.

"We have been searching for a marijuana antagonist for many years," said Dr. Martin, who has been a marijuana researcher for 22 years.

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NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

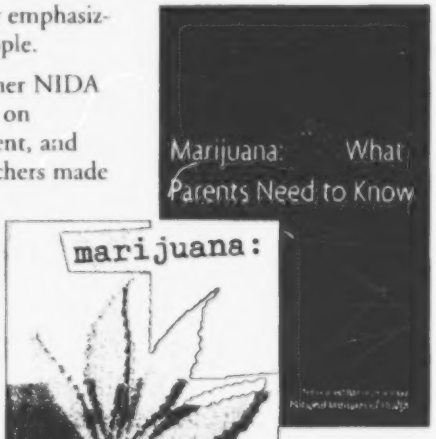
Volume 10, Number 4 (July/August 1995)

NIDA Takes a Lead Role in National Marijuana Initiative

By Neil Swan, *NIDA NOTES* Contributing Writer

NIDA is taking a lead role in the Marijuana Use Prevention Initiative announced by Health and Human Services Secretary Donna E. Shalala. The Institute is providing the scientifically based messages about marijuana that are designed to dispel myths, increase public awareness of rising trends in marijuana use among teens, and educate the public about the consequences of marijuana use, especially emphasizing the consequences for young people.

To kick off the Initiative, this summer NIDA sponsored the National Conference on Marijuana Use: Prevention, Treatment, and Research. Leading marijuana researchers made presentations on the consequences and effects of marijuana use, changing trends in its use, what it does to the body, and how marijuana use can progress from initiation to dependence or the use of other drugs. They discussed the effects of its psychoactive ingredient on the brain, on the disease-fighting immune system, and on children of women who smoke marijuana during pregnancy. They outlined how marijuana use, often in combination with alcohol, is associated with increased risks of auto accidents and the spread of AIDS.



NIDA is preparing question and answer booklets written for both parents and teenagers that present information to help correct widespread public misconceptions about marijuana use.

Keynote addresses for this first national conference focusing on marijuana were delivered by Secretary Shalala and Dr. Lee P. Brown, director of the White House Office of National Drug Control Policy, following a welcoming address by NIDA Director Dr. Alan I. Leshner.

To support the Marijuana Initiative, NIDA is also preparing science-based materials on how marijuana affects the brain, including learning and memory, and the body. The materials include question-and-answer booklets written for both parents and teenagers; a one-page fact sheet on the drug; "Marijuana Use: What Parents Can Do," a videotape for parents and other adults presenting science-based facts about marijuana; and a science education series for elementary school students. Advance copies of the booklets and a short version of the video were presented at the conference.

NIDA is working in collaboration with the Center for Substance Abuse Prevention and the Partnership for a Drug-Free America, a voluntary alliance of advertising agencies, in developing materials, videos, and programs to support the Secretary's Marijuana Use Prevention Initiative.

The Initiative was prompted last December when NIDA's Monitoring the Future survey reported disturbing trends showing increases in drug use among teenagers as young as 13.

The survey showed that, during the last 3 years, marijuana use among 8th-graders doubled and use among 10th- and 12th-graders increased significantly. "Current" use—within the past 30 days—of marijuana among high school seniors increased by 38 percent during the same period.

Along with increased use of marijuana and other drugs, the NIDA-sponsored survey also found a significant erosion in antidrug perceptions among young people. The proportion of those who believe occasional or regular marijuana use is harmful has declined by 22 percent over the last 3 years, according to the survey.

In announcing the Initiative, Secretary Shalala and other officials noted the proliferation of drug-culture images in movies and other media.

In addition to spearheading the Marijuana Initiative, the Institute is also expanding its marijuana research agenda with supplements to current research grants and a new marijuana research program announcement issued in July.

NIDA also continues to promote its antidrug campaign targeting teens and young adults. With the collaboration of the Advertising Council, the Institute is now producing the next phase of its "Get High, Get Stupid, Get AIDS" national media campaign. The campaign includes new TV announcements targeting both teens and young adults. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 10, Number 4 (July/August 1995)

Marijuana Initiative Features Scientifically Accurate, Credible Messages

By NIDA Director Dr. Alan I. Leshner

NIDA's most recent Monitoring the Future survey of teenage drug use revealed truly alarming trends. The survey of 8th-, 10th-, and 12th-grade students found drug use increasing in virtually all categories of drugs and at all age levels. Most disturbing to me was the finding that, for the third year in a row, there was a significant increase in marijuana use among 8th-grade students. Over the past 3 years, annual use of marijuana by 8th-graders has nearly doubled. In 1994, 13 percent said they had smoked marijuana at least once during the previous year.

These are 8th-graders—13-year-olds.

The NIDA-sponsored survey also found that antidrug perceptions were deteriorating. Fewer students than before now believe smoking marijuana occasionally—or even regularly—is harmful to their health.

Unless we, as a Nation, do something to correct teens' perceptions and the trend toward increasing levels in the use of marijuana and other drugs, we're headed for serious problems. Marijuana is often the introduction to progressive drug use patterns. For more than 20 years, NIDA-funded long-range studies repeatedly have shown that children and teenagers who use tobacco, alcohol, and particularly marijuana are at increased risk of using other drugs.

When Health and Human Services Secretary Donna E. Shalala announced the 1994 Monitoring the Future survey results last December, she called them an urgent warning of a disturbing trend in drug use among the country's adolescents. In response to this warning, she announced plans for the Secretary's Marijuana Use Prevention Initiative, a nationwide campaign to provide information to teens and parents that would counteract the drug-glamorizing messages our youth now receive from movies, TV, and pop music.

That Marijuana Initiative is now under way (see "NIDA Takes a Lead Role in National Marijuana Initiative"), and I am gratified that NIDA has been designated to play a key part in providing carefully crafted messages based on scientifically sound knowledge.

All of us involved in the campaign know it is critical that each of its messages be solidly based on scientific research findings. To be convincing to teenagers we must fully and honestly present the scientific evidence. And the information must be presented in ways that are readily understandable and convincing to adolescents and applicable to their world. This scientific documentation and communication are at the heart of NIDA's mission.

Media efforts, involving national TV networks and other print and broadcast media, will provide information on the dangers of marijuana use and how parents and children can address the problem in their homes, schools, and communities. The campaign is a joint effort in the Department of Health and Human Services involving the Office of the Secretary, NIDA, and the Center for Substance Abuse Prevention. The private sector is also involved, through the Partnership for a Drug-Free America, which makes available the communications expertise of major advertising agencies for public service campaigns against drug abuse.

NIDA has already prepared informational booklets for both parents and teens warning of the risks of marijuana use. Also in the works are a videotape, "Marijuana Use: What Parents Can Do," and a science-education series of materials for elementary school students.

The Marijuana Use Prevention Initiative will show young children, teenagers, and their parents that marijuana is a serious threat to the health and well-being of our youth. Too many parents—who may have themselves experimented with marijuana in their youth—often find it difficult to talk to their children about marijuana use or to lay out strict rules against its use.

But marijuana-use circumstances now are different from those remembered by today's parents. These parents should realize that today's children are starting marijuana use at a younger age and that more potent forms of the drug are now available. Parents need to understand that marijuana poses a serious threat to their children's vitality and potential. They need to tell their children not to use it.

The Initiative will show how marijuana is harmful by presenting the facts. Real-world scenarios based on scientific evidence will dramatize the risks involved with its use.

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For example, many people don't realize the extent to which marijuana can interfere with the physical and mental skills needed to safely drive a car, increasing the risk of auto accidents. Youngsters often drink beer or other alcoholic drinks while smoking marijuana, which increases still further the risk of automobile accidents.

As NIDA has already shown in its continuing nationwide media campaign for young people, "Get High, Get Stupid, Get AIDS," the Marijuana Initiative will show teens, in the language and media formats that they relate to, the high-risk connection between drug use and the spread of AIDS.

The messages will show children and teenagers that if they begin to use marijuana they become vulnerable to impairments in thinking, speaking, listening effectively, problem solving, and forming concepts. They will graphically demonstrate that marijuana can cripple the skills and functions they need to achieve their full potential or even to get a job. They will feature research showing that students do not retain knowledge when they are high from smoking a joint and that their motivation and cognition may be altered by marijuana, hampering their ability to learn.

We know that drug abuse is closely tied to increasing rates of crime and violence, family disintegration and related childhood developmental barriers, and death and disease—including the spread of AIDS. In its myriad manifestations, drug abuse can rob young people of their chance for a happy, healthy life. That's why we are undertaking this Initiative that targets an early, formative aspect of drug abuse—marijuana use among children and teenagers. NN

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Research Findings

Volume 10, Number 1 (January/February 1995)

NIDA Survey Provides First National Data on Drug Use During Pregnancy

By Robert Mathias, *NIDA NOTES* Staff Writer

More than 5 percent of the 4 million women who gave birth in the United States in 1992 used illegal drugs while they were pregnant, according to the first nationally representative survey of drug use among pregnant women. The NIDA-sponsored survey, which was released last fall, provides the best estimates to date of the number of women who use drugs during pregnancy, their demographic characteristics, and their patterns of drug use.

"Information from NIDA's National Pregnancy and Health Survey can help to guide public health policymakers who have to make decisions about prevention and treatment programs aimed at reducing the problem of drug abuse during pregnancy," said NIDA Director Dr. Alan I. Leshner. Dr. Leshner reported the survey's findings at a press briefing held during NIDA's conference on Drug Addiction Research and the Health of Women last September.

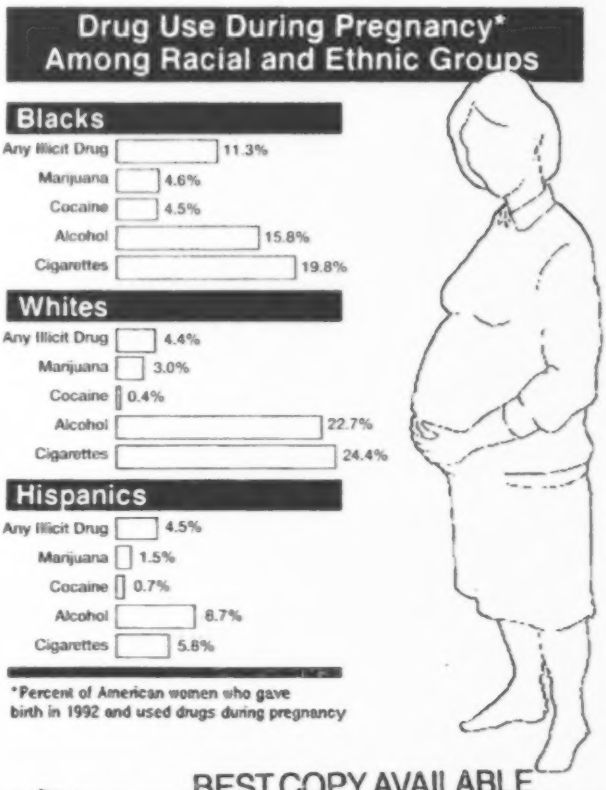
The survey gathered self-report data from a national sample of 2,613 women who delivered babies in 52 urban and rural hospitals during 1992. Based on these data, an estimated 221,000 women who gave birth in 1992 used illicit drugs while they were pregnant. Marijuana and cocaine were the most frequently used illicit drugs—2.9 percent, or 119,000 women, used marijuana and another 1.1 percent, or 45,000 women, used cocaine at some time during their pregnancy.

The survey found a high incidence of cigarette and alcohol use among pregnant women. At some point during their pregnancy, 20.4 percent, or 820,000, pregnant women smoked cigarettes and 18.8 percent, or 757,000, drank alcohol.

"We know for certain that these [legal] substances affect the health of the fetus and a woman during and after pregnancy," said Dr. Loretta D. Finnegan, NIDA's former senior advisor on women's issues. Health care practitioners should ask women about their use of cigarettes and alcohol during prenatal checkups and educate them about the health risks of licit drugs, said Dr. Finnegan, who now directs the Women's Health Initiative at the National Institutes of Health.

The survey also uncovered a strong link between cigarette smoking and alcohol use and the use of illicit drugs in this population. Among those women who used both cigarettes and alcohol, 20.4 percent also used marijuana and 9.5 percent took cocaine. Conversely, of those women who said they had not used cigarettes or alcohol, only 0.2 percent smoked marijuana and 0.1 percent used cocaine. "This finding reinforces the need for health practitioners to monitor the status of both licit and illicit drug use during pregnancy," said Dr. Leshner.

Besides providing the first national estimates of drug use during pregnancy, the survey also examined differences in the amount and types of drugs used by several racial and ethnic groups of women. Overall, 11.3 percent of African-American women, 4.4 percent of white women, and 4.5 percent of Hispanic women used illicit drugs while pregnant. While African Americans had higher rates of drug use, in terms of actual numbers of users, most women who took drugs while they were pregnant were white. The survey found that an estimated 113,000 white women, 75,000 African-American women, and 28,000 Hispanic women used illicit drugs during pregnancy.



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The survey found that an estimated 113,000 white women, 75,000 African-American women, and 28,000 Hispanic women used illicit drugs during pregnancy.

The survey also described different patterns of licit and illicit drug use among white women and ethnic minorities. African-American women had the highest rates of cocaine use, mainly "crack," during pregnancy. About 4.5 percent of African-American women used cocaine compared with 0.4 percent of white women and 0.7 percent of Hispanic women who did so.

White women had the highest rates of alcohol and cigarette use. Nearly 23 percent of white women drank alcohol and 24.4 percent smoked cigarettes. By comparison, 15.8 percent of African-American women and 8.7 percent of Hispanic women drank alcohol and 19.8 percent of African-American women and 5.8 percent of Hispanic women smoked cigarettes. "These findings point to the importance of attending to cultural issues in drug abuse prevention and treatment efforts," said Dr. Finnegan.

Although women who used drugs during pregnancy generally decreased their rates of drug use throughout their pregnancy, they did not discontinue drug use, Dr. Leshner noted. "This finding indicates how gripping an illness drug addiction can be, even in the face of what may seem to be the ultimate incentive to stay drug free," Dr. Leshner said. Nevertheless, "it is a disease that can be treated and managed with appropriate interventions," he stressed.

"With the information the survey provides about the patterns of drug use by women during pregnancy, we will be better able to identify priorities we must address," said Dr. Finnegan. This will enable researchers to develop and test more effective approaches to the differential drug abuse treatment and prevention needs of women of childbearing age, she concluded. NN

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Research Findings

Volume 10, Number 1 (January/February 1995)

Early Childhood Behavior and Temperament Predict Later Substance Use

By Neil Swan, *NIDA NOTES* Contributing Writer

By the first grade, or earlier, children show temperament and behavior traits that are powerful indicators of their inclination to use and abuse drugs in their teenage and adult years. Researchers have identified not only common childhood risk factors and behaviors that predict drug abuse potential but also protective factors that shield some children from influences to use drugs.

A number of long-range NIDA-funded studies have traced at-risk children into adulthood and parenthood, trying to determine why some children are able to resist persistent influences to use substances of abuse. Studies have zeroed in on several important factors in predicting a first-grader's subsequent use of substances: shyness, aggressiveness, rebelliousness, and gender. External risk factors include substance use among peers, drug use by parents, and troubles with the police. Protective factors include achievement in school or after-school activities and close family ties. The researchers are now designing drug abuse prevention and intervention strategies based on these findings made over 20 or more years.

Some of the earliest studies, by Dr. Margaret E. Ensminger and Dr. Sheppard G. Kellam and colleagues of Johns Hopkins University, started in the 1960s with first-graders and their families in Woodlawn, a poor, urban African-American community on the South Side of Chicago.

Today the researchers are following about 1,000 of the 1,242 original first-graders to continue to identify and monitor early childhood factors affecting later drug use and symptoms of psychiatric problems. These first-graders are now 32 or 33 years old.

Interviews in 1993 show that key risk factors such as aggressive behavior and shy-aggressive behavior identified 26 years ago continue to hold and are valid predictors of the subjects' current levels of cocaine use as adults.

During their studies, Dr. Ensminger and her colleagues rated each first-grader's mental health using two criteria: social adaptation and psychological health. To measure pupils' social adaptation to school, researchers used teachers' ratings of children's classroom social performance and intelligence as well as the results of standardized tests. Psychological health was determined by a number of criteria, including psychological symptoms, abnormal behavior, and level of self-esteem.

Two important risk factors identified as predictors of later drug use are shy behavior—described by the teachers as sitting alone, having few friends, and not speaking up in class—and aggression—described as fighting with others or breaking rules. Shyness and aggression are types of poor social adaptation distinct from symptoms of anxiety or depression, which are internal feelings, noted the researchers.

A number of long range NIDA-funded studies have traced at-risk children into adolescence and beyond trying to determine why some of them are able to resist influences to use substances of abuse

While shyness and aggressiveness are key predictors of drug use, a complex relationship exists between the two factors. Among boys, aggressive behavior in the first grade leads to increased teenage substance abuse, while first-grade shyness alone without aggressiveness leads to lower levels of substance abuse as teenagers. However, the combination of shyness and aggressiveness leads to even higher levels of adolescent substance use among boys than aggressiveness without shyness does, the studies found.

Boys whose teachers said they had problems concentrating in class had higher levels of later substance abuse because concentration problems appear to be closely related to aggressiveness, the studies reported. By contrast, neither aggressiveness, nor shyness, nor concentration problems in the first grade were associated with later substance use among girls.

Understanding Gender Differences

Shyness and aggressiveness may be less important predictors of substance use among females than among males because girls' peer groups are smaller and less important to them, she adds. These gender-based considerations are now being studied in drug abuse prevention programs, says Dr. Ensminger, who was among the first researchers to urge colleagues to stop dismissing gender as a possible key consideration in predicting children's subsequent drug use.

For both sexes, higher scores on first-grade IQ and readiness-for-school tests were associatedwith higher levels of beer or wine, hard liquor, and marijuana use 10 years later.

When the first-graders reached age 16 or 17, girls used smaller amounts of beer, wine, liquor, and marijuana and other illicit drugs but not cigarettes than boys did. For both sexes, higher scores on first-grade IQ and readiness-for-school tests were associated with higher levels of beer or wine, hard liquor, and marijuana use 10 years later, the researchers found. "This tells us that the children who are most ready for school are also those most ready to experiment with drugs," says Dr. Ensminger.

Psychological well-being and family relationships in the first grade seemed more important to girls than to boys in terms of influencing psychiatric symptoms 10 years later. Mothers had an important effect on the psychological status of their daughters but not of their sons. Mothers' expectations of how far daughters would go in school and mothers' own psychological health were positive factors in their daughters' psychological well-being 10 years later, the study found. Girls with strong family bonds tend to use drugs less than other girls do, but the same family influence is not so apparent with boys, said Dr. Ensminger.

Results from the Woodlawn study served as the basis for prevention programs started in Baltimore in the 1980s by Dr. Kellam and colleagues. That prevention effort focused on aggressive behavior because of its relationship to later drug use and on underachievement because of its relationship to depressed feelings.

Recent data gathered on the Woodlawn study subjects show that early childhood aggression is still a valid predictor of drug abuse when measured against the now-adult subjects' levels of use of cocaine, Dr. Ensminger reports. Those data are now being prepared for publication.

Examining Protective Factors

Another long-term study of drug-use predictors focuses on children in Northeastern States. For 20 years, Dr. Judith S. Brook of Mt. Sinai School of Medicine has studied risk factors identified in early childhood and in adolescence that are related to drug use during adolescence. She is conducting a study of 1,000 children and their mothers that began in 1975 in two communities representative of the population of the Northeastern United States. In the continuing research, Dr. Brook is examining not only risk factors but also protective factors that help shield children and adolescents from these risk factors.

Dr. Brook and her colleagues have identified a number of risk factors for subsequent drug use such as childhood aggression, which includes anger, aggression toward siblings, noncompliance, temper, and nonconforming behavior. Other risk factors are unconventionality—an attitude of deviance, rebelliousness, and evasion of responsibility—the extent of drug use among peers, and parental sociopathy, that is, parents' problems with drinking, drugs, or the police.

Dr. Brook's group examined the risk factors and their implications during childhood, ages 5 to 10; middle adolescence, ages 13 to 18; and late adolescence, ages 15 to 20. They found that childhood aggression and parental sociopathy predicted increased levels of drug use in late adolescence. They also determined that unconventionality during the early years of adolescence had an "important and pervasive impact on all aspects of middle and late adolescent functioning," including increased drug use.

The research team is now observing the original subjects' children, beginning at age 2, and interviewing both parents of these children to collect data on the new generation. "So we're now studying the third generation—the grandchildren of the mothers [of the original subjects] initially studied in 1975," says Dr. Brook. "And we're finding a great deal of consistency down through the generations in regards to personality and family characteristics," including traits that are drug-use risk factors.

The researchers also have studied interactions among risk factors and their implications for subsequent drug use as the children grow older. In addition to childhood aggression, they found three additional factors that influence late-adolescent drug use—unconventionality and drug use in middle adolescence and parental sociopathy during childhood. They found that little or no drug use in middle adolescence when combined with conventionality during the same age span resulted in the least amount of subsequent drug use.

As expected, parental sociopathy is related to late-teen drug use. Parents who drink or use drugs or both may be the most strict with their children, telling them, "Do as I say, not as I do," according to Dr. Brook's study. These admonitions might be effective in middle adolescence, when children are more likely to be influenced by parental demands, but not in later adolescence, when the family has less control and the parents' own display of negative behaviors becomes a drug-use risk factor, she says.

Dr. Brook agrees with other researchers that there are childhood protective factors that can be very powerful shields to safeguard children and adolescents from the recognized risk factors. These protective factors include achievement, religious commitment, strong family bonds, and a solid attachment to and emulation of a wholesome role model, she says.

"Some of these children are remarkably resilient," says Dr. Brook. Among those who become successful, she found evidence of protective factors such as church attendance, childhood achievement in school or in extracurricular activities, or close ties to brothers and sisters.

"Many of these kids go on to lead successful, productive lives, yet we tend to focus on the ones that don't," says Dr. Brook. "I want to learn more about what makes those that do well do so."

Family Relationships Critical

Still another continuing study of predictive factors for drug use focuses on a different population segment—at-risk children of white families living in small and medium-sized communities in Oregon. The study by Dr. Hyman Hops and colleagues of the Oregon Research Institute examines family and peer-group influences on adolescent substance use and is now in its 10th year. About 500 subjects were ages 11 through 15 at their first assessment in 1984 and will be 21 through 25 at their last assessment this year.

Among those studied, 90 percent of subjects who progressed from one substance of abuse to another did so in the following sequence—abstinence, alcohol, cigarettes, marijuana, and hard drugs. The most dramatic increase in drug use occurred between the ages of 13 and 14, when adolescents are going from middle to high school.

Parents' use of substances, including cigarettes, is an important predictive factor influencing their children's drug use. Within two-parent families, Dr. Hops found that fathers' drinking appears to have a greater impact than mothers' drinking on both girls and boys, while mothers' drinking has an effect only on adolescents under 14, before they enter high school. Parents who use cigarettes and alcohol may influence not only their children's use of the same substances but illicit substances as well, he says.

Family conflict and strife are strongly associated with increased substance abuse, based on the researchers' direct observations of problem-solving scenarios between parents and adolescents. Their findings suggest that families with substance-abusing children typically are unable to easily resolve problems and that the resulting confrontations negatively affect drug use.

In examining peer influences, the Oregon researchers balanced each study subject's self-reports of levels of substance use against reports of his or her substance use level from the child's best friend. The scientists reported that the amount of both family cohesion and peer encouragement to use drugs was predictive of initial levels of substance abuse. A good family relationship may play a powerful role as a protective factor in middle and late adolescence, they say. On the other hand, peer encouragement to use substances plays a stronger role across the age range and also suggests that early peer influences may encourage higher levels of drug use at later ages.

"These findings underscore the importance of family influences on substance abuse throughout adolescence and suggest greater attention to the family, as well as the peer group, in designing prevention strategies," says Dr. Hops. "You've got to have a healthy family relationship to counter the very powerful peer influences that kids face today."

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Printed July 2003

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